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A Comparison of Moderate Oral Sedation Drug Regimens for Pediatric Dental Treatment: A Pilot Study

Ojas A. Parikh
Virginia Commonwealth University

A Comparison of Moderate Oral Sedation Drug Regimens for Pediatric Dental Treatment: A Pilot Study

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Dentistry at Virginia Commonwealth University.

By

Ojas A. Parikh, DDS

BS, University of Maryland, College Park, 2009

DDS, University of Maryland School of Dentistry, 2015

Thesis Advisor: William O. Dahlke, DMD

Assistant Program Director, Associate Professor, Department of Pediatric Dentistry

Virginia Commonwealth University

Richmond, Virginia

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Abstract

A COMPARISON OF MODERATE ORAL SEDATION DRUG REGIMENS FOR PEDIATRIC DENTAL TREATMENT: A PILOT STUDY

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Purpose: Compare moderate oral sedation of pediatric patients using Hydroxyzine and Meperidine with either Diazepam or Midazolam in management of pediatric dental patients.

Methods: Randomized, double-blind, crossover pilot study of patients 3 to 7 years of age requiring two sedation visits. Frankl and Houpt behavior scores recorded at injection time, initiation of treatment and 100% oxygen at end of treatment. Postoperative phone call surveys conducted within eight hours and within 24 hours of discharge. Wilcoxon Signed-Rank tests, Fisher's Exact Chi-squared test and 0.10 significance level.

Results: 25 subjects completed 35 sedations. Eight participants completed both treatments and demonstrated significantly higher total Houpt Scores with Diazepam at all treatment stages. Frankl scores favored Diazepam at injection time. More abnormal behavior was found with Midazolam, less memory of the visit with Diazepam, but longer sleep time with Diazepam.

Conclusions: Sedation with the Hydroxyzine, Meperidine and Diazepam regimen may allow for a better overall sedation experience. Postoperative monitoring is essential. The results are promising and demonstrate the value of a larger study on sedation with Diazepam.

Introduction

Treating pre-cooperative and anxious children in the dental chair is challenging, requiring both skill and the appropriate tools for effective management.[1,2] When chairside behavior management techniques, which parents prefer, such as tell-show-do, voice control, nonverbal communication, positive reinforcement, and distraction are not effective, oral sedation is an effective option available to promote successful dental treatment.[3] Oral sedation is most accepted by pediatric patients, in comparison to intranasal, intravenous and intramuscular sedation.[4] Although mild, moderate and deep levels of sedation can all be induced by these medications, our focus will be on the medications used to provide moderate level sedation.

According to the American Academy of Pediatric Dentistry (AAPD), moderate oral sedation is the "drug-induced depression of consciousness" during which patients respond purposefully to verbal commands.[4] There is no intervention necessary to maintain an open airway, and spontaneous ventilation is adequate while cardiovascular function is maintained.[4,5] Patients medically qualified for moderate sedation must be relatively healthy with minimal obstruction of the airway to minimize adverse events. This is classified by the American Society of Anesthesiologists (ASA) as class I-II with a Brodsky tonsillar classification of 0-2. ASA I is a normal healthy patient with no systemic disease and ASA II is a patient with mild to moderate systemic disease that does not limit function[2,6–15]. Brodsky classification is the degree of tonsillar blockage of the oropharynx with maximum acceptance in oral sedation of Brodsky II, which is tonsillar blockage ranging from 25-50%.[3,10,16,17] Advantages of oral sedation in particular include reduced severity and incidence of adverse reactions, greater patient acceptance and compliance, cost, and convenience of administration. [12] Limitations of oral sedation include an inability to titrate the medications to desired effect given and its' unpredictability due to variable absorption

and first pass effects.[8,13,18,19] The onset and recovery may also be prolonged and variable because of individual variations in absorption which can delay patient discharge.[18] Administration of moderate sedation requires a sedation license, specialized training and an ability to rescue patients who have been sedated to a deeper level than intended.[10] Most adverse effects during pediatric dental anesthesia and sedation occurred when the sedation was done by general dentists who had little to no advanced training in anesthesia, did not monitor the vital signs of the patient during treatment and injected an excessive and toxic dose on local anesthetic because they did not weigh the patient prior to treatment.[7,20,21] Considering the potential significant risks of sedation, the benefits outweigh those risks when patient selection is ideal and sedation protocol is safely followed. According to the AAPD guidelines, vital signs (peripheral capillary oxygen saturation with pulse oximetry, respiratory rate, heart rate (HR), blood pressure (BP), and sometimes end-tidal CO2 with capnography) should be recorded at baseline, and every five minutes after dosing the patient with the sedation medication until treatment is complete and the patient is ready for discharge.

Oral sedation involves a wide spectrum of medications. Benzodiazepines such as Midazolam and Diazepam, antihistamines such as Hydroxyzine, opioids such as Meperidine, and Chloral Hydrate have been used individually or in combination for oral sedation in pediatric dentistry for years.[5] Nitrous oxide, an inhalation agent, is usually always used during oral moderate sedation for pediatric dentistry patients. The triple regimen of oral moderate sedation proves to be beneficial as the pharmacokinetics and pharmacodynamics help to minimize any potential side effect an individual medication may have. For example, Meperidine used alone can lower the seizure threshold and cause nausea and vomiting, however, when mixed with Hydroxyzine, with its antiemetic and antihistamine properties, and a Benzodiazepine, with its

anticonvulsant and amnesia properties, the side effects for Meperidine become minimal. Combinations frequently used for oral sedation include the Midazolam, Hydroxyzine and Meperidine combination as well as the Chloral Hydrate, Hydroxyzine and Meperidine combination.[22] Midazolam has been shown to be an effective tool for quick procedures due to its fast onset time, but may induce restlessness, agitation, anxiety and sometimes aggressive behavior. [23] Also, Chloral Hydrate lacks a reversal agent and as of May 2012, requires individual prescriptions per patient so it is no longer preferred by pediatric dentists as a medication for use in oral sedation.[17,24] Therefore an alternative to Midazolam or Chloral hydrate may be indicated in the sedation triple combination. Little research has compared the benzodiazepines, Midazolam with Diazepam, in combination with Hydroxyzine and Meperidine. If Diazepam, which is three to four times less potent than Midazolam, is substituted for Midazolam in such a combination, how would behavior and recovery change in a pediatric dental patient? To appreciate this, a better understanding of the individual medications is necessary.

Hydroxyzine is a medication with both antihistaminic and antiemetic effects. It causes Central Nervous System (CNS) depression, anxiolysis, analgesia, sedation and bronchodilation.[7,25–27] It's onset time is 15 to 30 minutes with 1.0 mg/kg orally, and it may potentiate the effects of Meperidine as well as other CNS depressants.[27] Meperidine is a narcotic analgesic which causes CNS, cardiovascular, and respiratory depression, produces sedation, analgesia, euphoria, and lowers the seizure threshold.[2] Onset time is 30 minutes, peak effect is at 1 to 2 hours, dosage ranges from 1 to 2 mg/kg orally and maximum dosage is 50 mg. Meperidine acts at the mu receptor, which functions as an inhibitory modulator of synaptic transmission in the CNS. One undesirable effect is that Meperidine can lead to non-immunologic histamine release. Therefore, combining it with Hydroxyzine will aid to counteract

this histaminic effect. Benzodiazepines are sedative/hypnotic agents which cause CNS depression and amnesia with minimal cardiovascular or respiratory effects.[28,29] They act on the limbic system, thalamus, and hypothalamus through mediation of the inhibitory neurotransmitter GABA.[30] Diazepam (Valium) has an onset time of 45 to 60 minutes and has a peak effect of 60 minutes.[31] It has a dosage of 0.25 to 0.3 mg/kg orally, with a max dose of 10mg.[32] However, Diazepam has a long half-life because it has multiple active metabolites.[12,30] Midazolam (Versed) has an onset time of 15 minutes with a peak effect at 30 minutes and working time of 30 to 40 minutes.[14] The dosage ranges from 0.5mg to 0.75mg, with a max dosage of 15mg.[9] It can be given via oral or intranasal administration and has fewer metabolites than Diazepam. Nitrous oxide is a titratable inhalation sedative used often in conjunction with the aforementioned medications to potentiate their effects and to assist in anxiolysis, sedation and analgesia.[10,13,17,19,22,33] The dosages of these medications are adjusted to minimize adverse effects when combined for oral sedation.

Ultimately, the goal is to promote cooperative behavior in order to safely complete dental treatment. Measuring behavior requires a standardized rating scale. The majority of oral sedation studies utilize one or both of the Frankl Scale, which is a global scale, and the Houpt Scale, which is a restricted scale.[34] The Frankl Scale, seen in Appendix 1, is used to measure overall behavior ranging from 1 to 4, with 1 being the worst behavior and 4 being the best behavior. The Houpt Scale, seen in Appendix 2, is divided into various categories including sleep, movement, and crying to allow for a more precise measurement in which lower scores mean poor behavior and higher scores mean better behavior. Behavior studies have shown that there is no correlation with poor behavior and previous dental treatment with oral sedation.[33] Due to sleepiness, drug-specific motor imbalance, and sleep during transit and recovery times greater

than four hours, “vigilant adult supervision” is recommended post-discharge.[20,35] Therefore, measurement of post-discharge behavior is just as important as behavior during treatment.

The purpose of this study is to compare the effect of the moderate oral sedation triple combination of Hydroxyzine and Meperidine with Diazepam or Midazolam in management of pediatric dentistry patients.

Materials and Methods

This study was a randomized double blind observational study of moderate oral sedation treatment conducted at the Virginia Commonwealth University (VCU) School of Dentistry, Department of Pediatric Dentistry. The protocol was approved by the VCU Institutional Review Board, Committee on Human Research (VCU IRB# HM20006549) on June 16th, 2016.

Subject Selection Criteria

Following a power analysis for statistical significance, 25 participants between the ages of 3 and 7 who were already treatment planned for oral moderate sedation from the VCU Dental School, Department of Pediatric Dentistry were enrolled in the study for completion of two or more quadrants of dentistry. Following the VCU School of Dentistry's standard of care and American Academy of Pediatric Dentistry (AAPD) guidelines, patient participants for oral moderate sedation must have an ASA classification of I or II, present with history of fearful or refractory behavior at previous dental visits documented by Frankl Scores of 1-3, and tonsillar hypertrophy less than 50% characterized by Brodsky rating of 0 to 2. Patients are required to obtain a history and physical examination by the primary care physician for clearance for oral sedation. In addition, all participants are required to have fasted (NPO, *nil per os,* nothing by mouth) midnight prior to the scheduled oral sedation visit. All consents and assents for the study were signed by the guardians and participants the morning of the first oral sedation treatment.

Exclusion criteria for patients in this study include severe systemic disease, allergy to the sedation and anesthetic medications used for treatment, nasal obstruction, recent upper respiratory infections, limited neck movement, obesity, macroglossia, and tonsillar hypertrophy

greater than 50%. According to the AAPD Sedation Guidelines, "children in ASA classes III and IV, children with special needs, and those with anatomic airway abnormalities or extreme tonsillar hypertrophy present issues that require additional and individual consideration and therefore, practitioners are encouraged to consult with appropriate subspecialists." Thus, those patients were excluded from this study to avoid the risk of any complications.

Procedure

All participants were randomly assigned to be first treated with the Diazepam triple regimen or the Midazolam triple regimen. The participants' second visit was with the alternative triple combination with identical dosage of Hydroxyzine, Meperidine and Nitrous Oxide as the first visit to allow the individual to serve as his or her own control. The pediatric dentistry resident and faculty attending were aware of the triple combinations given, however, the sedation monitor, participant and parent were blind to the combination given for treatment. The reversal agents for both combinations were the same, Flumazenil for the benzodiazepines (Diazepam and Midazolam) and Naloxone for Meperidine. Calculations based on the child's weight of maximum local anesthetic delivery, oral sedation medication dosages and reversal agents were done prior to delivery of medication.

The Diazepam triple regimen included Diazepam, Hydroxyzine and Meperidine, and the Midazolam triple regimen included Midazolam, Hydroxyzine and Meperidine. Each of the medications used were marketed and approved by the FDA for use orally, and for use in combination with other medications. The medication dosages were tailored individually based on the participant's weight as follows:

<u>Diazepam Triple Regimen</u>

1. Meperidine (Demerol)- narcotic/opioid, 1.0-2.0mg/kg, 50 mg max

2. Hydroxyzine HCl (Atarax)- antihistamine, 1.0-2.0mg/kg, 50 mg max

3. Diazepam (Valium)- benzodiazepine, 0.1-0.3mg/kg, 10 mg max

Midazolam Triple Regimen

1. Meperidine (Demerol)- narcotic/opioid, 1.0-2.0mg/kg, 50 mg max

2. Hydroxyzine HCl (Atarax)- antihistamine, 1.0-2.0mg/kg, 50 mg max

3. Midazolam (Versed)- benzodiazepine, 0.2-0.3mg/kg, 10 mg max

Vital signs (SpO2, respiratory rate, HR, BP and EtCO2) were recorded at the start of the procedure and every five minutes afterwards until treatment was complete and the patient was ready for discharge. Nitrous oxide was administered at concentrations ranging from 30 to 50%. Behavior was evaluated by the monitor at injection time, start of procedure and when 100% oxygen was administered at the completion of treatment using the Houpt Scale and Frankl Score. The Houpt Scale comprises of scores in relation to sleep, movement, crying and overall behavior.

Upon completion of treatment, a popsicle was given to ensure that the participant had intact reflexes and was adequately hydrated. The patient was discharged when they met the discharge criteria per AAPD Guidelines. These criteria include: airway patency is satisfactory and stable, patient is easily arousable, responsiveness is at or near pre-sedation level, protective reflexes are intact, patient can talk, patient can sit up unaided, and state of hydration is adequate. Postoperative instructions were explained to the guardian and participant and the participant was escorted via wheelchair to their car.

The guardian answered yes or no questions during postoperative phone calls made eight hours and 24 hours after discharge regarding the participant's behavior in the car ride home and

upon arrival home. Questions regarding sleep, memory, activity level, motor imbalance, nausea, and emesis were asked. Those guardians who answered both sets of questions after both sedation treatments were sent a check of $25.00 as a sign of appreciation for participation.

All pediatric dental residents and faculty involved were certified in Pediatric Advanced Life Support (PALS) and Basic Life Support (BLS) training. Also, emergency management training was conducted biannually. All personnel who participated as sedation monitors were calibrated for Houpt and Frankl scoring prior to the study to ensure accuracy and consistency of study measures.

Results

Statistical Methods

Data was summarized using descriptive statistics. Differences among categorical variables were compared using Fisher's Exact Chi-squared test. Difference in behavior measures and post-operative time spent sleeping were compared using Wilcoxon signed-rank tests. All analyses were performed in SAS EG v.6.1 with a pilot study significance level of 0.10.

Results

A total of 25 subjects were enrolled in the study. A total of 35 sedation visits were completed. Eight of the 25 patients successfully completed treatment under both sedation methods. Of these eight, five had their initial sedation with Diazepam and the remaining three started with Midazolam. A summary of the participation is given in Table 1. Demographics of all participants and the subset with both visits are given in Table 2. There were no differences in demographics between those who did and did not complete both sedations in terms of age, gender, ethnicity, insurance type, locale, or treatment order.

Of the 35 attempted sedations, there were a total of eight failures. Three of the eight occurred with the Diazepam and the remaining five were with Midazolam, resulting in failure rates of 18% for Diazepam and 28% with Midazolam. However, this difference was not statistically significant (p-value=0.6933). Additionally, two patients had to be excluded from the second sedation because all treatment was completed during the first visit. Both of these cases were completed with the Diazepam triple regimen. Seven patients failed to follow-up for the second visit.

Behavior Scores

Behavior scores were compared at injection time, treatment time, and 100% oxygen administration at end of treatment for those who completed both treatments. A significance level of 0.10 was used given the limited sample size and nature of the pilot study. Complete breakdown of the scores are given in Table 2. Median scores were higher for Diazepam than Midazolam for all measures, though not all differences were statistically significant. Frankl scores were significantly different at injection time (p-value=0.0625). The median Frankl score for Midazolam was 3 compared to 4 for Diazepam. Total Houpt scores were significantly different at all treatment stages (injection, initiation of treatment, and 100% oxygen administration at end of treatment). Median Houpt scores were higher for Diazepam than Midazolam for all treatment stages (injection: 15.5 vs 13.5; initiation of treatment: 16 vs 13; 100% oxygen administration: 16 vs 14). Overall behavior scores were significantly different at injection and initiation of treatment, but not at 100% oxygen administration at end of treatment. At injection time, the median overall behavior score was 6 for Diazepam compared to 5 for Midazolam (p-value=0.0625). At initiation of treatment, the median score was 6 for Diazepam compared to 4.5 for Midazolam (p-value=0.0625). The higher the Frankl and Houpt behavior scores, the more cooperative the study participant.

Side Effects

Parents were contacted within the first eight hours after discharge and questioned about their child's behavior. A summary of side effects reported are given in Table 3. Parents reported more, though not statistically significant, abnormal behavior with Midazolam (43% vs 14%; p-value=0.1573) and significantly less memory of the visit for Diazepam (43% vs 86%; p-value=0.0833). Parents also reported longer sleeping times when returning home with Diazepam than Midazolam (81.4 minutes vs 30 minutes), though this was not statistically significant (p-

value=0.3125).

Parents and guardians were also contacted at 24-hours after discharge, but due to lack of response from a majority of parents, there was insufficient data to analyze.

Discussion

Oral moderate sedation is an essential tool when other behavior management techniques are ineffective. The results from this study show that moderate sedation with the Diazepam triple regimen containing both Hydroxyzine and Meperidine is more effective than the Midazolam regimen during treatment, and resulted in less undesirable effects after treatment. Previous studies have compared many different oral moderate sedation regimens for pediatric dentistry, however no literature to date has been published comparing the combinations used in this pilot study.

Studies have been conducted comparing the benzodiazepines Midazolam and Diazepam, as single agents in the past. One found no statistical difference between the sedation effect of oral Midazolam to oral Diazepam[36] while another found that Midazolam was more effective in regulating patient behavior at times of increased stimulation (papoose board, rubber dam, injection time).[37] One study also found that oral diazepam had no influence on behavior management for dental treatment, which is contraindicatory to research claiming it does improve behavior management.[31] These contraindicatory findings indicate the need for further study.

Overall comparison suggests that the Diazepam regimen is the more favorable of the two. Of the 25 participants who consented to the study, eight successfully completed treatment with both regimens. Five of the eight had their initial sedation with Diazepam while three started with Midazolam. A total of 35 sedations were completed, of which there were eight failures due to uncooperative behavior. Three of those failures were with Diazepam (18%) while five were with Midazolam (28%), this difference was not statistically significant (p-value=0.6933).

Furthermore, two of the 25 participants had all of their treatment completed in the first treatment with the Diazepam regimen because their behavior was so good it allowed for all treatment to be completed. Therefore, this study revealed more failures with the Midazolam regimen and more successful completions of treatment with the Diazepam regimen. This may have clinical implications for pediatric dentists when selecting medication regimens for moderate sedation of pediatric patients including more effective and predictable sedations, fewer failures, better overall experience for the child, and better financial production for the dentist with the Diazepam regimen.

Behavior was recorded at three treatment stages including injection time, initiation of treatment, and at 100% oxygen administration at the end of treatment. Diazepam was favored over Midazolam. Higher Frankl and Houpt scores generally indicate more favorable behavioral outcomes. Frankl scores for injection time were statistically significant, favoring Diazepam (p-value = 0.0625). Total Houpt scores were higher with Diazepam than Midazolam for all treatment stages (injection: 15.5 vs 13.5; initiation of treatment: 16 vs 13; 100% oxygen administration: 16 vs 14). The overall behavior scores were statistically significant at injection time and initiation of treatment, favoring Diazepam. There was no statistical significance for overall behavior during 100% administration and this may be due to lack of stimulation that would likely elicit poor behavior. At injection time, the median Houpt score was six for Diazepam and five for Midazolam (p-value=0.0625), while at initiation of treatment, the median score was six for Diazepam compared to 4.5 for Midazolam (p-value=0.0625). These results show that during treatment, the Diazepam regimen may be a better option during the treatment stages resulting in less movement, less crying, and more somnolence. A very challenging part of pediatric dental treatment is the delivery of local anesthetic, which can foreshadow the degree of

patient cooperation for the remainder of treatment. In this study, the Frankl score was significantly higher with the Diazepam triple during the injection procedure which is clinically relevant for pediatric dentists, since majority of the failed sedations failed at injection time.

In addition to treatment outcomes, results also suggested a difference in post-discharge side effects. Parents were contacted within eight hours of discharge, and answered post discharge questions over the phone. Although not statistically significant, more abnormal behavior was reported with Midazolam vs. Diazepam (43% vs. 14%) and less memory of the visit was reported with Diazepam vs. Midazolam (43% vs 86%). A concern for Diazepam is the longer half-life, which may have resulted in the longer sleep times noted upon arrival at home with an average of 81.4 minutes with Diazepam vs. 30 minutes with Midazolam. However, this result was not statistically significant (p-value of 0.3125). Though Diazepam seems to be the better regimen during treatment, concerns over longer half-life are very important for post discharge criteria, emphasizing the need for attentive supervision by parents in transportation to and at the patient's home. This is particularly important since Diazepam was used in combination with two other medicaments, both of which can prove to have potentiating effects and varying times of lasting effect.

Safety is the main priority when sedating young children and therefore, all treatment providers were certified in Basic Life Support (BLS) and Pediatric Advanced Life Support (PALS). Medication dosage calculations were specific to the participant's weight and the sedation protocol met the standards for both VCU Pediatric Dentistry and the AAPD guidelines. A data safety and monitoring plan was implemented and any adverse event was recorded every month, however all adverse events were mild involving routine repositioning of safety monitors such as the pulse oximeter, for accurate readings. Most adverse effects during oral sedation,

according to the literature, occur due to a lack of compliance with AAPD sedation monitoring guidelines, and overdosing on local anesthetic.[7] Our study did not result in any adverse effects requiring medical attention or initiation of emergency protocol. There were instances where treatment was aborted due to poor behavior which could have resulted in compromising the safety of the study participant and of the study personnel. In such circumstances, patients were worked up for treatment under general anesthesia. Adverse events including airway obstruction, allergic reactions, bronchospasm, laryngospasm, respiratory depression, hypoxia and hypercarbia did not occur in this study.

There are concerns surrounding the notion that a previous sedation visit could affect patient behavior for future sedation treatments. A 2002 study in *Pediatric Dentistry* found no correlation with poor behavior and previous dental treatment with oral sedation.[33] Our study, in particular, did not test this however it is something that we can focus on in future studies.

Despite numerous attempts to contact the participants, there was a high no-show and cancellation rate. Of the 25 participants, seven failed to come for their second sedation visit. Reasons for the high cancellation rate may include recent illness such as an upper respiratory infection which elicits a four-to-six-week postponement per AAPD guidelines, scheduling conflicts, an inability to communicate with parents due to altered contact information, or an inability to meet parent's expectations for the visit. For future studies, a better incentive plan can be implemented which may help to retain more participants.

This pilot study had several limitations. The three to seven-year age range limited the number of participants in the study, while the age range could have been divided into multiple ranges from ages 1-6, 6-12 and greater than 12.[32] The participant pool was primarily insured by Medicaid and were of African American ethnicity from an urban locale, which is representative

of our clinic population but not necessarily of a general population. The high sedation failure rate may be because this study was conducted in a residency program where many of the patients already have difficult behavior problems. In addition, ideally, the same resident or faculty member would have monitored the Frankl and Houpt behavior scores to ensure consistency in calibration, however, lack of personnel was a significant limitation. All residents are calibrated for scoring upon entrance into the program, however no inter-rater agreement was done. Postoperative surveys were challenging as the guardians often did not pick up the phone call, or another relative or babysitter was monitoring the child at home while the guardian left for work after discharge.

Future studies should incorporate a larger sample size of participants with a wider age range comprising of an equal distribution of demographics and a larger number of personnel. Better patient selection and more consistent behavior scoring methods may be indicated, possibly with video recording of treatment to better rank behavior, or dual-monitoring with two providers scoring patients and inter-rater testing. More focus on post discharge side effects may be of greater significance as attentive adult supervision is essential after discharge especially with Diazepam due to its longer half-life and Midazolam due to its effects on abnormal behavior and difficulty of walking.[20,35] Also, a future study comparing the two benzodiazepine combinations with and without nitrous oxide may be of interest.

Conclusion

Sedation with the Diazepam regimen may allow for a better experience for the pediatric dental patient, the parent and doctor in comparison to the Midazolam regimen. The long half-life of Diazepam is still a concern for sedation so proper monitoring by parents is essential during travel to and at the patient's home. Results from this study are promising and demonstrate value of a larger study on treatment with the Diazepam regimen.

Tables

Table 1: Study Participation

Study Participation	n (%)
Enrolled	25 (100%)
Failed First Visit	7 (28%)
All Treatment Completed Visit 1	2 (8%)
Completed Both Visits	8 (32%)
Drop-outs	8 (32%)

Table 2: Demographics

Demographics	Total Sample (n=25)	Completed Study (n=8)	P-value*
Age (mean, SD)	5.4 (1.41)	5.5 (1.31)	0.8142
Gender			1.0000
Male	15 (60%)	5 (63%)	
Female	10 (40%)	3 (38%)	
Race/Ethnicity			0.1674
African American	14 (56%)	3 (38%)	
Asian American	1 (4%)	1 (13%)	
Caucasian	7 (28%)	4 (50%)	
Hispanic	2 (8%)	0 (0%)	
Middle Eastern	1 (4%)	0 (0%)	
Insurance Type			0.6237
Medicaid	19 (76%)	7 (88%)	
Private Insurance	6 (24%)	1 (13%)	
Locale			1.0000
Urban	20 (80%)	7 (88%)	
Rural	5 (20%)	1 (13%)	
Treatment Order			0.6728
Midazolam-Diazepam	12 (48%)	3 (38%)	
Diazepam-Midazolam	13 (52%)	5 (63%)	

*p-value from t-test or chi-squared test, as appropriate

Table 3: Median Behavior Scores by Treatment

	Median			
	Midazolam	**Diazepam**	**P-value***	
Frankl				
Injection	3	4	0.0625	†
Treatment	3	4	0.2500	
Oxygen	3.5	4	0.2500	
Houpt				
Houpt: Sleep				
Injection	2	2	0.6250	
Treatment	2	2	0.5000	
Oxygen	2	2	0.3750	
Houpt: Movement				
Injection	3	4	0.2188	
Treatment	3	4	0.3125	
Oxygen	3.5	4	0.5000	
Houpt: Crying				
Injection	3	4	0.5000	
Treatment	3.5	4	0.2500	
Oxygen	4	4	0.5000	
Houpt: Total				
Injection	13.5	15.5	0.0625	†
Treatment	13	16	0.0781	†
Oxygen	14	16	0.0313	†
Overall				
Injection	5	6	0.0625	†
Treatment	4.5	6	0.0625	†
Oxygen	5	6	0.1250	

*P-value from Wilcoxon Signed-Rank Test

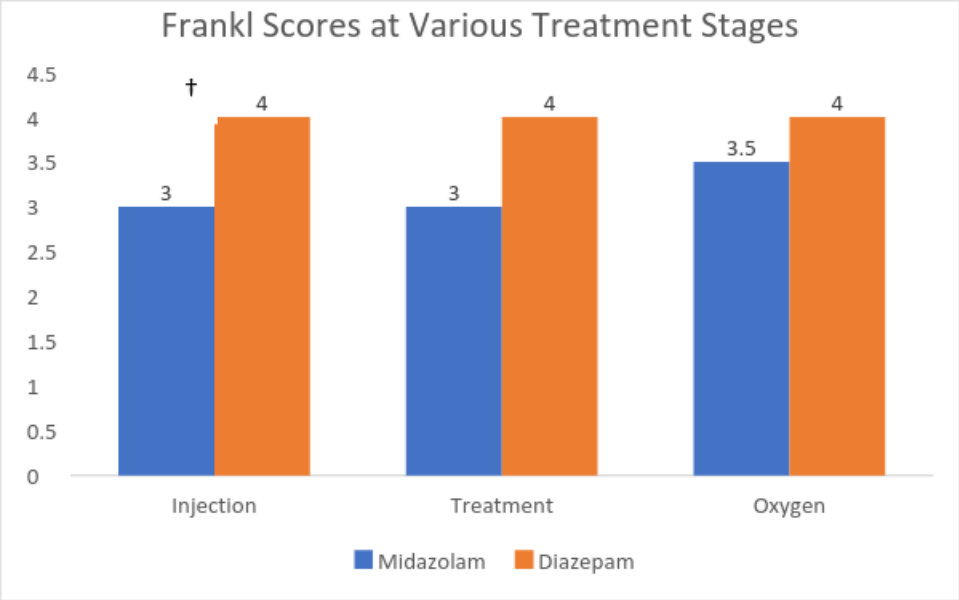
†Indicates significant difference at 0.10 level

Table 4: Post-Op Phone Call Survey

	Midazolam	**Diazepam**
Abnormal Behavior	3 (43%)	1 (14%)
Difficulty Walking	1 (14%)	0 (0%)
Dizziness	1 (14%)	1 (14%)
Nausea	0 (0%)	1 (14%)
Remember Visit	6 (86%)	3 (43%)
Play at Home	2 (29%)	0 (0%)
	Midazolam	**Diazepam**
Time Slept (Mean, SD)	30 (45.83)	81.4 (80.71)

Figures

Figure 1: Frankl Scores at Various Treatment Stages



†Indicates significant difference at 0.10 level

Figure 2: Median Houpt Scores at Various Stages by Sedation Medication

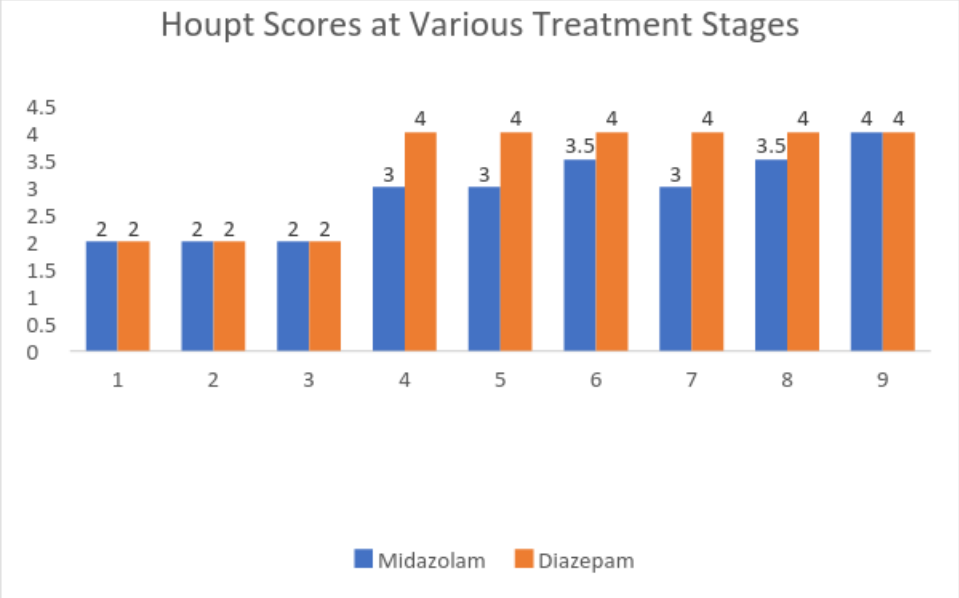
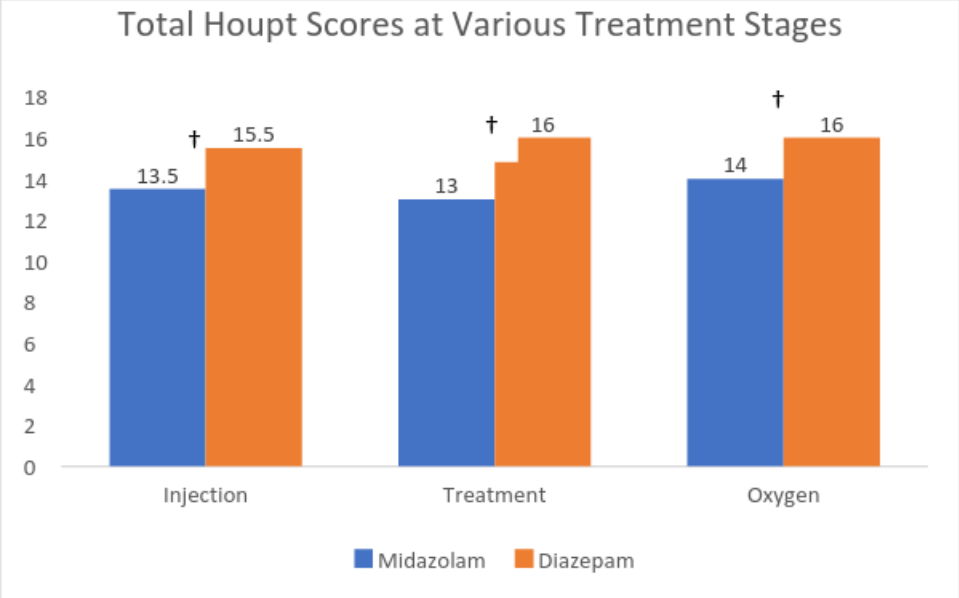
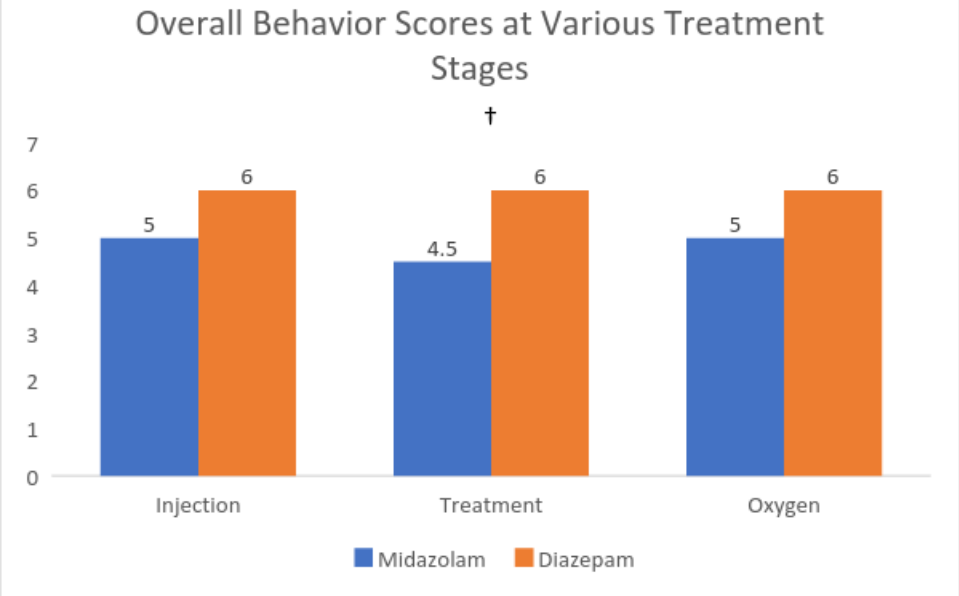


Figure 3: Median Total Houpt Scores by Treatment Stage and Medication



†Indicates significant difference at 0.10 level

Figure 4: Median Overall Behavior Scores by Treatment Stage and Medication



†Indicates significant difference at 0.10

Appendix 1: Frankl Behavior Scale

Rating	Description
1 (--) Definitely Negative	Refuses treatment, cries forcefully, extremely negative behavior associated with fear
2 (-) Negative	Reluctant to accept treatment and displays evidence of slight negativism
3 (+) Positive	Accept treatment, but if the child has a bad experience during treatment, may become uncooperative
4 (++) Definitely Positive	Unique behavior, looks forward to and understands the importance of good preventive care.

Appendix 2: Houpt Behavior Scale

Houpt Scale	Description
Rating for sleep	
1	Fully awake, alert
2	Drowsy, disoriented
3	Asleep
Rating for movement	
1	Violent movement interrupting treatment
2	Continuous movement making treatment difficult
3	Controllable movement that does not interfere with treatment
4	No movement
Rating for crying	
1	Hysterical crying that demands attention
2	Continuous, persistent crying that makes treatment difficult
3	Intermittent, mild crying that does not interfere with treatment
4	No crying
Rating for overall behavior	
1	Aborted- no treatment rendered
2	Poor- treatment interrupted, only partial treatment completed
3	Fair- treatment interrupted, but eventually all completed
4	Good-difficult, but all treatment performed
5	Very good- some limited crying or movement, e.g., during anesthesia or mouth prop in
6	Excellent- no crying or movement

Appendix 3: Behavior Scale Rating Sheet

Procedure	Frankl Score	Behavior Category	Houpt Rating
Injection Time		Sleep	
		Movement	
		Crying	
		Overall Behavior	
		Total	
Initiation of Treatment		Sleep	
		Movement	
		Crying	
		Overall Behavior	
		Total	
100% Oxygen via nasal hood post-treatment		Sleep	
		Movement	
		Crying	
		Overall Behavior	
		Total	

Appendix 4: Post-Op Phone Call Survey

Post Op Phone Call	Yes	No
Questions:		
Did your child:		
1. Exhibit any abnormal behavior?		
2. Fall asleep on the car ride home?		
Does your child normally sleep in car?		
Did your child snore?		
Does your child usually snore?		
Was it difficult to awaken your child when you arrived home?		
3. Sleep soon after arriving home?		
4. Did your child snore?		
Does your child usually snore?		
5. Have difficulty walking?		
6. Complain of or seem dizzy?		
7. Play immediately after arriving home?		
8. Have any memory of what happened at the dental office?		
9. Complain of nausea?		
10. Vomit?		
Did your child consume any liquids or foods before vomiting?		
11. Have an upset stomach?		
How long did they sleep after arriving home?	# minutes _____	

Appendix 5: Sedation Medications Used

Medication	Concentration	Manufacturer
Diazepam oral solution	5mg/ml	Roxane Laboratories
Diazepam tablet	5mg	Mylan Inst.
Meperidine oral solution	50mg/5ml	Roxane Laboratories
Midazolam syrup	2mg/ml	Roxane Laboratories
Hydroxyzine tablet	25mg	Pfizer
Hydroxyzine syrup	10mg/5ml	Silarx Pharmaceuticals, Inc.
Nitrous oxide		Airgas USA, LLC (Puritan Medical)

Literature Cited

1. Golpayengani M, Dehghan F, Ansari G, Shayeghi S. Comparison of oral Midazolam-Ketamine and Midazolam-Promethazine as sedative agents in pediatric dentistry. *Dent Res J (Isfahan)*. 2012;9(1):36-40.

2. Lenahan M, Wells M, Scarbecz M. A Retrospective Study of 248 Pediatric Oral Sedations A Retrospective Study of 248 Pediatric Oral Sedations Utilizing the Combination of Meperidine and Hydroxyzine for Dental Treatment. *J Clin Pediatr Dent*. 2015;39(5):481-487.

3. McCormack L, Check J-W, Trapp L, Job A. A Comparison of Sedation-related Events for Two Multiagent Oral Sedation Regimens in Pediatric Dental Patients. *Pediatr Dent*. 2014;36(4):302-308. doi:10.3171/2009.8.JNS09516.

4. AAPD. *Pediatric Dentistry Reference Manual*.; 2016.

5. Wilson S, Houpt M. Project USAP 2010: Use of Sedative Agents in Pediatric Dentistry- a 25-year Follow-up Survey. *Pediatr Dent*. 2016;38(2):127-133.

6. Canpolat DG, Yildirim MD, Aksu R, Kutuk N, Alkan A, Cantekin K. Intravenous ketamine, propofol and propofol-ketamine combination used for pediatric dental sedation: A randomized clinical study. *Pakistan J Med Sci*. 2016;32(3):682-687. doi:10.12669/pjms.323.9834.

7. Chicka MC, Dembo JB, Mathu-Muju KR, Nash DA, Bush HM. Adverse events during pediatric dental anesthesia and sedation: a review of closed malpractice insurance claims. *Pediatr Dent*. 2012;34(3):231-238. doi:10.1016/0090-4295(93)90521-B.

8. Nelson TM, Xu Z. Pediatric dental sedation: Challenges and opportunities. *Clin Cosmet Investig Dent*. 2015;7:97-106. doi:10.2147/CCIDE.S64250.

9. Salem K, Kamranzadeh S, Kousha M, et al. Two Oral Midazolam Preparations in Pediatric Dental Patients: A Prospective Randomised Clinical Trial. *Int J Pediatr*. 2015:1-7. doi:10.1155/2015/349795.

10. Cote CJ, Wilson S. Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016. *Pediatr Dent*. 2016;38(4):E13-E39.

11. Al-Zahrani A, Wyne A, Sheta S. Comparison of oral midazolam with a combination of oral midazolam and nitrous oxide-oxygen inhalation in the effectiveness of dental sedation for young children. *J Indian Soc Pedod Prev Dent*. 2009;27(1):9-16. doi:10.4103/0970-4388.50810.

12. Sebastiani FR, Dym H, Wolf J. Oral Sedation in the Dental Office. *Dent Clin N Am*. 2016;60:295-307. doi:10.1016/j.cden.2015.11.002.

13. Musani IE, Chandan N V. A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. *Eur Arch Paediatr Dent*. 2015;16:417-424. doi:10.1007/s40368-015-0187-7.

14. Done V, Kotha R, Vaas AAK, Sahana S, Jadadoddi RK, Bezawada S. A Comparison of the Effectiveness of Oral Midazolam-N2O versus Oral Ketamine- N2O in Pediatric Patients- An in-Vivo Study. *J Clin Diagnostic Res*. 2016;10(4):ZC45-ZC48. doi:10.7860/JCDR/2016/16760.7592.

15. Lourenço-Matharu L, Papineni McIntosh A, Lo JW. Predicting children's behaviour during dental treatment under oral sedation. *Eur Arch Paediatr Dent*. 2016;17:157-163. doi:10.1007/s40368-015-0205-9.

16. Martinez D, Wilson S. Children sedated for dental care: a pilot study of the 24-hour postsedation period. *Pediatr Dent*. 2006;28(3):260-264. http://www.ncbi.nlm.nih.gov/pubmed/16805359.

17. Merrell DW. Comparison of oral ketamine-midazolam and chloral hydrate-meperidine-hydroxyzine sedation regimes in pediatric dentistry. *Virginia Commonw Univ VCU Sch Compass*. 2013.

18. Fallahinejad Ghajari M, Ansari G, Soleymani AA, Shayeghi S, Fotuhi Ardakani F. Comparison of Oral and Intranasal Midazolam/Ketamine Sedation in 3-6-year-old Uncooperative Dental Patients. *J Dent Res Dent Clin Dent Prospects*. 2015;9(2):61-65. doi:10.15171/joddd.2015.013.

19. Dionne R a, Yagiela J a, Coté CJ, et al. Balancing efficacy and safety in the use of oral sedation in dental outpatients. *J Am Dent Assoc*. 2006;137(April):502-513. doi:10.1093/jjco/hyq252.

20. Dosani F, Flaitz CM, Whitmire Jr HC, Vance BJ, Hill JR. Postdischarge Events Occuring after Pediatric Sedation for Dentistry. *Pediatr Dent*. 2012;36(5):411-416.

21. Wilson TD, McNeil DW, Kyle BN, Weaver BD, Graves RW. Effects of conscious sedation on patient recall of anxiety and pain after oral surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;117(3):277-282. doi:10.1016/j.oooo.2013.11.489.

22. Wilson S, Nathan JE. A Survey of Sedation Training in Advanced Pediatric Dentistry Programs: Thoughts of Program Directors and Students. *Pediatr Dent*. 2011;33(4):353-361.

23. Gazal G, Fareed WM, Zafar MS, Al-Samadani KH. Pain and anxiety management for pediatric dental procedures using various combinations of sedative drugs: A review. *Saudi*

Pharm J. 2014;24(4):379-385. doi:10.1016/j.jsps.2014.04.004.

24. Avalos-Arenas V, Moyao-García D, Nava-Ocampo AA, Zayas-Carranza RE, Fragoso-Ríos R. Is chloral hydrate/hydroxyzine a good option for paediatric dental outpatient sedation? *Curr Med Res Opin*. 1998;14(4):219-226. doi:10.1185/03007999809113362.

25. Gladney M, Stanley RT, Hendricks SE. Anxiolytic activity of chloral hydrate and hydroxyzine. *Pediatr Dent*. 1994;16(3):183-189.

26. Fallahinejad Ghajari M, Vahid Golpayegani M, Bargrizan M, Ansari G, Shayeghi S, Fallahinejad Ghajari M. Sedative Effect of Oral Midazolam/Hydroxyzine versus Chloral Hydrate/Hydroxyzine on 2-6 Year-Old Uncooperative Dental Patients: A Randomized Clinical Trial. *J Dent*. 2014;11(1):93-99.

27. Wilson S. Management of child patient behavior: Quality of care, fear and anxiety, and the child patient. *Pediatr Dent*. 2013;35(2):170-174. doi:10.1016/j.joen.2012.11.040.

28. Tyagi P, Dixit U, Tyagi S, Jain A. Sedative Effects of Oral Midazolam, Intravenous Midazolam and Oral Diazepam. *J Clin Pediatr Dent*. 2012;36(4):383-388.

29. Danion J-M, Zimmermann M-A, Willard-Schroeder D, Grang~ D, Singer L. Diazepam induces a dissociation between explicit and implicit memory. *Psychopharmacology (Berl)*. 1989;99:238-243.

30. Ashton H. Guidelines for Rational Use of Benzodiazepines. *Drugs*. 1994;48(1):25-40.

31. Kantovitz KR, Puppin-Rontani RM, Gaviao MBD. Sedative effect of oral diazepam and chloral hydrate in the dental treatment of children. *J Indian Soc Pedod Prev Dent*. 2007;June:69-75.

32. Mittal N, Goyal A, Jain K, Gauba K. Pediatric Dental Sedation Research: Where Do We Stand Today? *J Clin Pediatr Dent*. 2015;39(3):284-291.

33. McComb M, Koenigsberg SR, Broder HL, Houpt M. The effects of oral conscious sedation on future behavior and anxiety in pediatric dental patients. *Pediatr Dent*. 2002;24(3):207-211. http://www.ncbi.nlm.nih.gov/pubmed/12064492.

34. Wilson S. A review of important elements in sedation study methodology. *Pediatr Dent*. 1995;17(7):406-412.

35. Paryab M, Afshar H, Mohammadi R. Informing Parents about the Pharmacological and Invasive Behavior Management Techniques Used in Pediatric Dentistry. *J Dent Res Dent Clin Dent Prospects*. 2014;8(2):95-100.

36. Tyagi P, Tyagi S, Jain A. Sedative effects of Oral Midazolam, Intravenous Midazolam and Oral Diazepam Sedative effects of Oral Midazolam, Intravenous Midazolam and Oral

Diazepam in the Dental Treatment of Children. *J Clin Pediatr Dent*. 2013;37(3):301-305.

37. Pisalchaiyong T, Trairatvorakul C, Jirakijja J, Yuktarnonda W. Comparison of the effectiveness of oral diazepam and midazolam for the sedation of autistic patients during dental treatment. *Pediatr Dent*. 2005;27(3):198-206.