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Comparison of Triple Combination Oral Sedation Regimens for Pediatric Dental Treatment

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Comparison of Triple Combination Oral Sedation Regimens for Pediatric Dental Treatment

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

By

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Abstract

A COMPARISON OF TRIPLE COMINATION ORAL SEDATION REGIMINES FOR PEDIATRIC DENTAL TREATMENT

By: Brett Henderson, DMD

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Virginia Commonwealth University, May 2019

Thesis Advisor: William O. Dahlke, DMD

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Purpose: Compare the efficacy of two benzodiazepines (diazepam or midazolam) in combination with meperidine and hydroxyzine for pediatric dental sedation.

Methods: A randomized, double blind observation study of behaviors and outcomes related to two sedation groups. Frankl and Houpt behavior scores were recorded at three time points: injection time, initiation of treatment and at the end of treatment. Postoperative phone call surveys were conducted within eight hours of discharge to assess sleep, activity, and behavior.

Results: A total of 40 sedation subjects were included in the study, of which 20 were treated with diazepam triple Combination (Di+M+H) and 20 with midazolam triple regime (Mi+M+H). Treatment was successful for 45% of cases with midazolam and 70% with diazepam (*P* value=.20). Houpt sleep scores were significantly higher for diazepam than midazolam at

injection (*P*-value=.0043) and during treatment *(P*-value=.0152). Although Frankl scores, Houpt move and Houpt cry scores tended to favor diazepam, none were statistically significantly different. More abnormal behavior was reported with midazolam, though not statistically significant (35% vs 6%, *P*-value=.0854). Postoperative sleep time was longer for midazolam, but not significantly different (median sleep time: 61 vs 45 minutes, *P*-value=.2071).

Conclusion: The diazepam, meperidine, hydroxyzine triple combination sedation regimen shows promising results as a successful alternative to midazolam triple combination. Longer postoperative monitoring may be required with diazepam, but this study has shown postoperative sleep times to be less than previously reported. Larger sample size is needed to determine if the current trend will be maintained.

Introduction

Triple combination sedation regimens have been a mainstay in pediatric dentistry for many years to allow for moderate sedation of pre-cooperative and anxious pediatrics patients.[1] Over the years, the drug combinations have changed, with the current triple combination of midazolam, meperidine, and hydroxyzine being the most studied and widely accepted form of triple combination as a result of the ability to reverse both the opioid and benzodiazepine drugs in the event of adverse reactions.[2]

Prior to the midazolam triple, chloral hydrate with hydroxyzine and meperidine was the triple regimen of choice, but without a reversal drug for chloral hydrate, higher rates of emesis, and increased likelihood of respiratory depression, alternatives were sought to improve efficacy and safety.[3,4] Studies of midazolam across numerous delivery routes and drug combinations in pediatrics have been linked with agitation[3], yet there is significant research claiming that oral versed is a superior or equal pediatric sedative when compared with oral diazepam.[5]

To date, there is little evidence comparing midazolam versus diazepam in a triple combination sedation.[2] One of the primary reasons for studying the various combinations of benzodiazepine triple regimens is related to the history of midazolam extrapyramidal and paradoxical effects related to agitation and hyperactivity, both are believed to be linked to the rapid uptake and quicker half-life of midazolam, i.e. faster withdrawal symptoms.[6] A 2012 Cochran review showed a weak effectiveness for midazolam, and with the increase incidence of general anesthesia for pediatric dental procedures, many practitioners are reducing the amount of

pediatric oral sedation procedures.[2,7] These issues pose the dilemma of discovering a better alternative to the current triple combination therapy.

When using a modern triple combination sedation regimen, a narcotic such as meperidine is used for pain control in conjunction with an antiemetic/antihistamine such as hydroxyzine, along with a sedative benzodiazepine such as midazolam or diazepam. Each of these medications alone may produce sedative effects and when used in combination may potentiate even greater sedative effects.[8–12] Meperidine is a synthetic opioid analgesic that causes central nervous system (CNS), cardiovascular, and respiratory depression. It is a mu receptor agonist that primarily produces analgesia and sedation that can lower seizure threshold and induce histamine release. Oral meperidine analgesia can be obtained within 15 minutes of administration; peak analgesia onset is 60-120 minutes with a half-life of 2.5 to 5 hours.[11,13–15] Therapeutic doses of meperidine (1 - 2mg/kg) may induce euphoria & reduce shivering, while excessive doses may induce dysphoria and convulsions.[15] Hydroxyzine is a H1 antagonist providing antihistamine, antipruritic, and antiemetic properties. Hydroxyzine is considered a sedative, CNS depressant and may provide relief from anxiety, itching, skeletal muscle relaxation, analgesia, and bronchodilation. Hydroxyzine oral onset is 15-30 minutes, maximum clinical effects takes place by 2 hours, with a duration of sedative effects lasting 3 to 4 hours, finally the half-life of antipruritic effects are 14-20 hours.[8,12,16,17]

Benzodiazepines achieve their CNS depressant anxiolytic effect by positive allosteric modulation of the gamma amino butyric acid $(GABA)_{A.}$ receptor that is a ligand- gated chloride-selective ion channel. GABA is the most common CNS inhibitory neurotransmitter; which reduces excitability of neurons and produces a calming effect on the brain, especially in the limbic, hypothalamic, and thalamic systems which are associated with behavior and emotion. [8,18]

Midazolam is a water-soluble short acting, high potency benzodiazepine that provides sedative, anxiolytic, amnestic, and hypnotic effects. Oral peak onset is 10-20 minutes with a half-life 2.2 to 6.8 hours. The major metabolite is α-hydroxymidazolam and is considered to be just as potent as midazolam. Diazepam is a lipid soluble long acting, medium potency benzodiazepine that provides anxiolytic, muscle relaxing, anticonvulsant, and amnestic effects. The oral (*per os*, PO) peak onset is 30-90 minutes with a half-life of ~18 hours in children 3 to 8 years old. There are multiple active metabolites of diazepam with the major metabolites being desmethlydiazepam, temazepam, and oxazepam, which are associated with the prolonged half-life of diazepam[9]. Midazolam is considered to be 1.5 to 2 times more potent than diazepam and has a higher risk of adverse respiratory events.[8–10,14,15,17–19] This potency is related to the water solubility of midazolam; midazolam is a low pH racemic solution of open and closed ring forms of the drug; once midazolam is systemically absorbed, it rapidly converts to a lipophilic closed ring (physiologically active) form of midazolam and has two times the affinity for $GABA_A$ receptors than diazepam.[10,20,21]

The primary concern with using diazepam is related to its long elimination half-life, but what is often overlooked is the blood brain distribution (sedation) half-life, which is 2 hours compared to midazolam's distribution half-life of 1 hour.[19,22] Distribution half-life accounts for onset and duration of sedation; following absorption, serum concentrations are high and the drug will be distributed to tissues into degree of perfusion: brain, muscle, and then adipose. As drug distribution proceeds, serum levels decline, and high concentrations in the brain redistribute into the blood stream and into subsequent other tissues. These processes occur more rapidly with highly lipid soluble drugs and account for the shorter duration of sedation seen in both midazolam and diazepam.[14,19] Drug elimination half-life is more closely associated with water

solubility, which is why midazolam (water soluble) has a significantly shorter elimination half - life when compared with diazepam (lipid soluble) due to quicker processing by the liver and less active metabolites.[14,20]

The emotions of fear and anxiety often hold the behaviors of aggression and hostility in check, but the ingestion of a benzodiazepine or other anxiolytic drugs may produce a paradoxical increase in aggression once GABA inhibition has provided an anxiolytic effect.[8,17] Midazolam's higher affinity for GABA receptors causes chloride channels to remain open longer, which increases the accumulation of GABA on the presynaptic clefts, which could subsequently induce extrapyramidal effects as the drug wears off.[16,20] Any sedative anxiolytic could have side effects of agitation and irritability, however diazepam may reduce these adverse reactions due to its higher affinity for GABA antianxiety sub-receptors and has even been used to treat midazolam agitation reactions when reversal drugs (flumazenil) have previously failed to improve such agitations & combativeness.[21,23] Such agitations with behavior may be the difference between successfully completing treatment or aborting the sedation.[24] Preoperative diazepam has been shown to show less emergence agitation from general anesthesia when compared with preoperative midazolam.[25] Nathan and Vargas reported higher agitation rates with higher single doses of midazolam and lower rates of agitation with lower doses of midazolam in combination with high dose meperidine and longer working time.[26] These side effects (inconsolable crying, restlessness, and agitation)[27] may be linked with less than harmonious sedations and may alter parents' perceptions of how the overall sedation experience was for their child.[28]

Much of the sedation research does not address the rates of agitation, irritability, intra-operative & post-operative behavior, & routinely does not account for adequate working time of oral diazepam.[29] Diazepam has been reported to treat hallucinations, tremors, alcohol

withdrawals, midazolam withdrawal agitation, and to reduce general anesthesia emergence agitations.[23,25] Considering these benefits of diazepam and its reduced risk of respiratory depression, a further look at its efficacy in pediatric dental sedation as a midazolam alternative is needed.

In 2016, Parents rated sedation as the most acceptable form of advanced behavior guidance techniques.[30] Promoting cooperative behavior is the ultimate goal of sedation in order to safely complete dental treatment.[31] The majority of oral sedation studies utilize one or both of the Frankl Scale, and the Houpt Scale as their standardized rating scales. The Frankl Scale is used to measure overall behavior ranging from one to four, with one being the worst behavior and four being the best behavior (Appendix 1).[32] The Houpt Scale 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 (Appendix 2).[33]

The purpose of this study is to compare the effect of the moderate oral sedation triple combination of hydroxyzine and meperidine with either diazepam or midazolam in the management of pediatric dentistry patients both intra-operatively and in the post-operative period.

Definition of Terms

1) **Midazolam Triple = *Mi*+*M*+*H* = Midazolam, Meperidine, Hydroxyzine triple combination regimen**
2) **Diazepam Triple = *Di*+*M*+*H* = Diazepam, Meperidine, Hydroxyzine triple combination regimen**

Methods

This study was a randomized double-blind study of moderate oral sedation for dental treatment conducted at the Virginia Commonwealth University (VCU) School of Dentistry, Department of Pediatric Dentistry. This Protocol was approved by the VCU Institutional Review Board, Committee for Human Research as VCU IRB HM20006549-Amendment 3 on April 3, 2018.

Sample Criteria

This study was an amended update to a pilot study at VCU, which was conducted with a smaller sample size.[34] In this study, we strived to have a larger sample size while comparing patients during their first sedation appointment only. Forty participants between the ages of three and seven who are already treatment planned for oral moderate sedation were enrolled in the study for completion of their dentistry from June 2017 through February 2019. Patient participants for oral moderate sedation must have an ASA classification of I or II with tonsil hypertrophy less than 50% as characterized by Brodsky ratings of zero to two. Patients with refractory or fearful behavior documented by Frankl scores of 1 to 3 and Frankl 4 patients with significant dental needs (greater than 2 quadrants) and a history of dental anxiety were included in this study.

Patients were required to obtain a history and physical examination by their primary care physician for oral sedation clearance and be fasting (*nil per os*, NPO) after midnight of the morning of sedation as required by VCU Pediatric Dentistry protocol. Consents for the sedation and study participation were completed on the morning of the sedation appointment.

Exclusion criteria for patients in this study, as also outline by the American Academy of Pediatric Dentistry (AAPD) guidelines for oral sedation[35], 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%, ASA classes III or greater, special needs patients, and those with anatomic airway abnormalities or extreme tonsillar hypertrophy present issues that require additional considerations. These patients were excluded from this study to decrease the risk of any complications and allow for better standardization of medication dosing.[14,35]

Procedure

Participants were randomly assigned for sedation with either the diazepam triple regimen or the midazolam triple regimen for their first sedation only: 20 patients for each treatment group. The randomization list was determined using random number generator in SAS EG v6.1 to randomize the order of 20 patients for each treatment group in random blocks of 10. If the participants needed a second visit, the second sedation was not studied to allow for optimization based off of their previous sedation history. The pediatric dental 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 are 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:

Diazepam Triple Regimen

1. Meperidine (Demerol) - narcotic/opioid, 1.5-2.0mg/kg, 50 mg max
2. Hydroxyzine HCl (Atarax) - antihistamine, 1.5-2.0mg/kg, 50 mg max
3. Diazepam (Valium) - benzodiazepine, 0.2-0.3mg/kg, 10 mg max[17,29]

Midazolam Triple Regimen

1. Meperidine (Demerol) - narcotic/opioid, 1.5-2.0mg/kg, 50 mg max
2. Hydroxyzine HCl (Atarax) - antihistamine, 1.5-2.0mg/kg, 50 mg max
3. Midazolam (Versed) - benzodiazepine, 0.5-0.75mg/kg, 15 mg max[26,36,37]

Vital signs (oxygen saturation, respiratory rate, heart rate, non-invasive blood pressure and end-tidal CO_2) were monitored at the start of the procedure and every five minutes afterwards until treatment was complete and the patient was ready for discharge. Nitrous oxide with oxygen was administered at concentrations ranging from 30% to 70%, as determined by provider for each child to potentiate the effects of the oral medications to attempt the desired level of sedation. Behavior was evaluated using the Houpt Scale (Appendix 2) and Frankl Score (Appendix 1) by the monitor at three time points: 1) injection time, 2) start of procedure and 3) when 100% oxygen was administered at the completion of treatment (Appendix 3). Analysis of the various treatment checkpoints and group types include Wilcoxon rank-sum test and chi-squared test. For standardization of this study, treatment was initiated between 45 to 60 minutes after dosing to allow for adequate onset of meperidine and hydroxyzine, while also accounting for the patients' level of sedation and behavior.[38] Nitrous oxide was administered after 5 minutes

of 100 percent pre-oxygenation and was titrated to effect as deemed necessary by the provider for the procedure.

The patients were discharged once they met the discharge criteria per AAPD Guidelines which 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.[35] Postoperative instructions were explained to the guardian and participant and the patient was escorted via wheelchair to their car.

A postoperative phone call survey was completed within eight hours after discharge regarding the participant's behavior in the car ride home and upon arrival home (Appendix 4). The questions included inquiry about sleep, memory, activity level, motor imbalance, nausea, emesis, and behavior.

All pediatric dental residents and faculty involved are certified in Pediatric Advanced Life Support (PALS) and Basic Life Support (BLS) training. Also, emergency management training is conducted biannually. All personnel who participate 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 rank-sum tests. All analyses were performed in SAS EG v.6.1 with a significance level of 0.05. P-values between 0.05 and 0.10 were deemed marginally statistically significant.

Results

A total of 40 subjects were enrolled in the study, with equal allocation to midazolam (n=20) and diazepam (n=20). Demographics of all participants are given in Table 1. There were no significant differences between the two groups in terms of age (p-value=0.4903) or gender (p-value=0.7440).

Of the 40 attempted sedations, there were a total of 17 failures. Eleven of the 17 occurred with the midazolam triple and the remaining six were with diazepam triple. Resulting in failure rates of 30% for diazepam and 55% with midazolam, though this difference was not statistically significant (p-value=0.20). Failure was defined as aborted treatment, or deviation of treatment that lead to placement of sodium diamine fluoride, sedative fillings, or general anesthesia workup even if some of the planned treatment was successfully completed.

Behavior Scores

Behavior scores were compared at injection, treatment, and procedure completion. Complete breakdowns of the scores are given in Table **2**. Median scores were higher for diazepam triple than midazolam triple for all measures, though not all differences were

statistically significant. Frankl scores (Figure 1) were marginally significantly different at treatment initiation (p-value=0.0792) and procedure completion (p-value=0.0984). Houpt Sleep scores (Figure 2) were significantly higher for diazepam at injection (1 vs 2; p-value=0.0043) and treatment (1 vs 2; p-value=0.0152), but not at procedure completion (1 vs 2; p-value=0.3537). Houpt Movement (Figure 3) scores were marginally higher for diazepam at treatment (2 vs 3; p-value=0.0670), and at oxygen (2 vs 3; p-value=0.0753), but not at injection (2 vs 3; p-value=0.2428). There were no differences in Houpt Crying scores at any of the time points (p-value>0.4). Total Houpt scores (Figure 4) were marginally significantly different at all time points (injection (p-value=0.1077), treatment (p-value=0.0877), oxygen (p-value=0.0825)). Total Houpt scores were higher for diazepam than midazolam for all time points (injection: 8.5 vs 13; treatment: 8 vs 12.5; oxygen: 10 vs 14). Overall behavior scores (Figure 5) were significantly higher for diazepam at oxygen (2.5 vs 4.5; p-value=0.0470).

Side Effects

Guardians were contacted within the first eight hours after discharge and questioned about the child's behavior. A total of 33 guardians were reached and provided information regarding postoperative side effects (17 with midazolam and 16 with diazepam). A summary of the side effects reported is given in Table 3 and Figure 6. Guardians reported marginally more abnormal behavior with midazolam (35% vs 6%; p-value=0.0854) and more difficulty walking (41% vs 13%; p-value=0.0822). Guardians reported significantly more sleeping in the car on the ride home for midazolam (71% vs 38%; p-value=0.0526). Guardians also reported that children treated with midazolam were significantly more likely to complain of or seem dizzy (36% vs 0%; p-value=0.0184). Guardians also reported an estimated time the child slept (including car ride home and after arriving home). The estimated median total time slept was 45 minutes for

diazepam (IQR: 0-90 minutes) and 61 for midazolam (IQR: 25-120 minutes). Although guardians tended to report longer sleep times with midazolam, the difference was not statistically significant (p-value=0.2071).

Discussion

Previous studies comparing benzodiazepines as single agents have noted statistical differences between the sedation effects of midazolam versus diazepam[5]; midazolam has shown to have a higher first pass effect, very short half-life, and higher potency (1.5-2 times more potent) when compared to diazepam.[20] Studies regarding anesthesia induction have concluded that preoperative midazolam for pediatric anesthesia induction, sedates patients deeper, while diazepam is better at reducing anesthesia emergence agitation.[25] Diazepam has a longer half-life that can remain in the system up to 48 hours, however the clinical effects of procedural sedation typically last for no more than 2 hours and have a tendency to transition patients into a more calming anti-anxiety state.[16,17,21,22] The results from this study do show that moderate sedation with diazepam triple did result in more procedural sleep and resulted in more successful treatment outcomes. One could argue, that the midazolam triple was not as effective due to the midazolam wearing off sooner, however our data showed median total Houpt scores for midazolam triple were highest at the completion of procedure (Figure 4) and if the wait times were shorter then we could have seen longer post-operative midazolam sleep times. The crucial times in sedation when the patients are most likely to fail is at the time of injection and at the initiation of treatment due to placement of the rubber dam, dry-field isolator, or due to the unpleasant sounds of the dental handpiece. During these two treatment phases, sleep was statistically significantly higher for diazepam and the data overall consistently showed higher scores for diazepam at all time points and variables measured. Parental perception of how the

appointment went may be dictated by how their child's mood appears once they return to the room after the procedure is complete. At the completion of the procedure, diazepam triple's Houpt overall behavior was significantly greater (Figure 5). The postoperative surveys showed that with the VCU dosing protocols, patients slept less after discharge with diazepam triple combination than with midazolam triple combination. The data did reflect our suspicions regarding the negative side effects of midazolam including restlessness, incidences of agitation, hallucination, and abnormal behavior, but was only marginally significant (Figure 6). At this time there is significant research, supporting the use of midazolam, yet the higher drug cost, potential for paradoxical effects, and existing literature appear to be conflicting with VCU's current Diazepam triple combination protocol & clinical success rates.

Our study included several limitations, which could be improved upon in future studies. This study took place in a teaching residency and involved various resident dental operators and multiple resident sedation monitors. All of the residents were calibrated for behavior scoring at multiple times during the study, which included their entrance into the residency program, one week prior to study initiation, 3 months into the study and at the 6 month study time, however no inter-rater agreement was done for scoring. Ideally, the same resident or faculty member would have monitored the behavior scores for all of the sedations, however attempting to coordinate this within the residency program proved to be a cumbersome task and was not pursued. Another consideration for improving rater consistency would involve video tapping of the sedations and having multiple raters assess the behavior of each sedation blind to the drug regimen. The age range of our study population, age 3 to 7, limited the number of study participants, but if future studies were to expand the age range, then we would recommend

comparing sedation outcomes within the various age groups.[2] The postoperative phone calls proved to be challenging due to difficulty getting in touch with the guardians, and sometimes the guardian left the child to be watched by another relative or babysitter while returning to work, which lead to incomplete data for the postoperative phase of treatment.[34] Higher sedation failure rates could be attributed to the lack of consistent provider between the sedation workup appointment and the sedation appointment within the residency program. As training pediatric dental residents, assessing childhood behavior and gauging a child's ability to cooperate with the planned dental sedation versus general anesthesia is an art and takes time to hone and may also account for the higher sedation failure rates.

Future studies should include larger sample size, wider range of age, an equal distribution of demographics, with more consistent operator and monitor personnel. Diazepam's longer half-life suggests that greater emphasis is needed toward studying the postoperative effects as well as the attentive adult supervision necessary regarding midazolam's effects on difficulty walking, respiratory depression, and abnormal behavior.[4,17,19,28] Retrospective studies regarding diazepam triple and midazolam triple may provide better insight into the overall success of these regimens, rates of adverse events, trends in pre and postoperative dental visit behavior, assessing average treatment working times, determining average post-operative monitoring times, treatment completion rates, and post-operative sleep times.

Conclusion

The diazepam, meperidine, hydroxyzine triple combination sedation regimen shows promising results as a successful alternative to midazolam triple combination. Longer postoperative monitoring may be required with diazepam, but this study has shown postoperative sleep times to be less than previously reported. A larger sample size is needed to determine if the current trend will be maintained.

Tables

Table 1: Sample Demographics

	Midazolam (n=20)	Diazepam (n=20)	Total (n=40)	P-value*
Age (mean, SD)	5.4, 1.35	5.1, 1.32	5.3, 1.3	0.4903
Gender (n, %)				
Male	7, 35%	8, 40%	15, 38%	0.7440
Female	13, 65%	12, 60%	25, 63%	

*P-value from t-test or Chi-squared test

Table 2: Median Behavior Scores by Treatment

	Midazolam (n=20)	Diazepam (n=20)	P-value*
Frankl			
Injection	2 (1.5, 3)	3 (2, 4)	0.1903
Treatment	3 (1, 3)	3.5 (2, 4)	0.0792
Oxygen	2 (1, 2)	3 (1.5, 4)	0.0984
Houpt			
Houpt: Sleep			
Injection	1 (1, 1.5)	2 (1, 3)	0.0043
Treatment	1 (1, 2)	2 (1, 2)	0.0152
Oxygen	1 (1, 2)	2 (1, 2)	0.3537
Houpt: Movement			
Injection	2 (1.5, 3)	3 (2, 3.5)	0.2428
Treatment	2 (1, 3)	3 (2, 3.5)	0.0670
Oxygen	2 (2, 3)	3 (3, 4)	0.0753
Houpt: Crying			
Injection	3 (2, 4)	3.5 (2, 4)	0.8672
Treatment	2 (2, 4)	3 (2, 4)	0.5748
Oxygen	3 (2, 4)	3.5 (2.5, 4)	0.4701
Houpt: Total			
Injection	8.5 (7.5, 12)	13 (8, 15)	0.1077
Treatment	8 (6.5, 13)	12.5 (8, 15)	0.0877
Oxygen	10 (6.5, 12)	14 (9.5, 15)	0.0825
Overall			
Injection	3 (2, 4)	4 (2.5, 5)	0.1517
Treatment	3 (1, 5)	4 (2.5, 5)	0.1442
Oxygen	2.5 (1, 4.5)	4.5 (2.5, 5.5)	0.0470

*P-value from Wilcoxon Rank Sum Test

†Indicates significant difference at 0.10 level

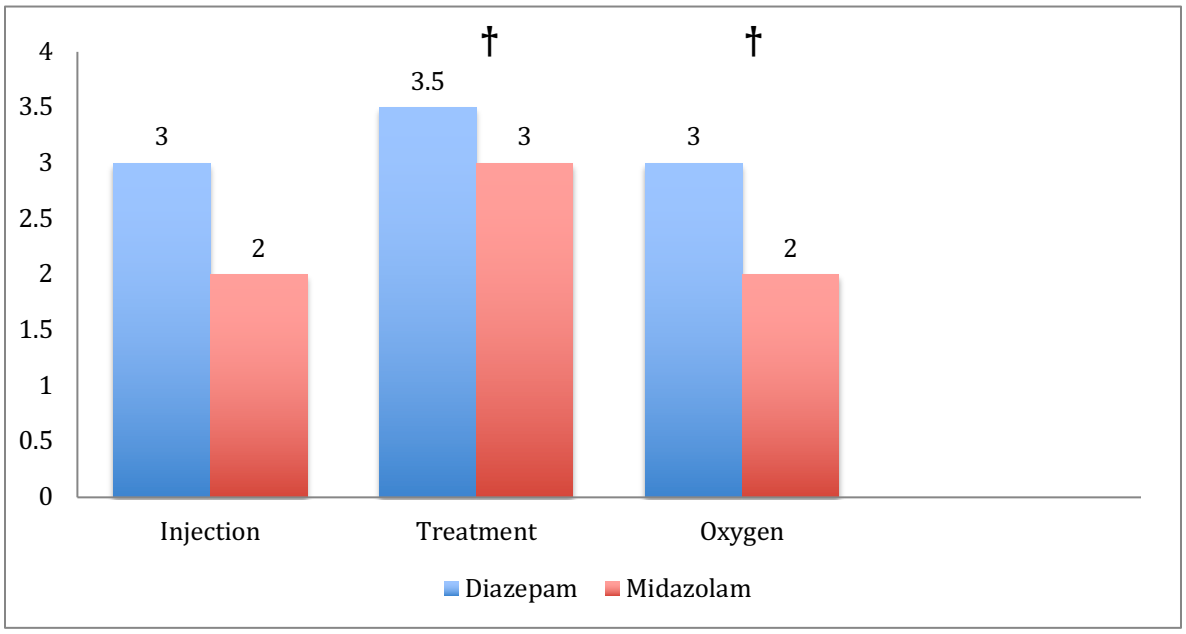
Table 3: Side Effects Reported by Guardians at 8 Hour Post Op Call

	Midazolam (n=20)	Diazepam (n=20)	P-value*
Exhibit Any Abnormal Behavior	6, 35%	1, 6%	0.0854
Fall asleep on the car ride home	12, 71%	6, 38%	0.0526
Did your child snore (in car)?	2, 12%	0, 0%	0.4848
Was it difficult to awaken your child when you arrived home?	3, 18%	0, 0%	0.2273
Sleeping at Home	10, 59%	6, 38%	0.3028
Did your child snore (at home)?	0, 0%	1, 6%	0.1026
Have difficulty walking	7, 41%	2, 13%	0.0822
Complain of or seem dizzy?	6, 36%	0, 0%	0.0184
Play at Home	4, 24%	8, 50%	0.1571
Have any memory of what happened in the dental office?	5, 29%	2, 13%	0.1577
Nausea	3, 18%	1, 7%	0.6029
Vomit	0, 0%	0, 0%	N/A
Have an upset stomach?	1, 6%	1, 6%	1.0000

*P-value from Fisher's Exact Test; N/A where no events were reported and therefore no test was conducted

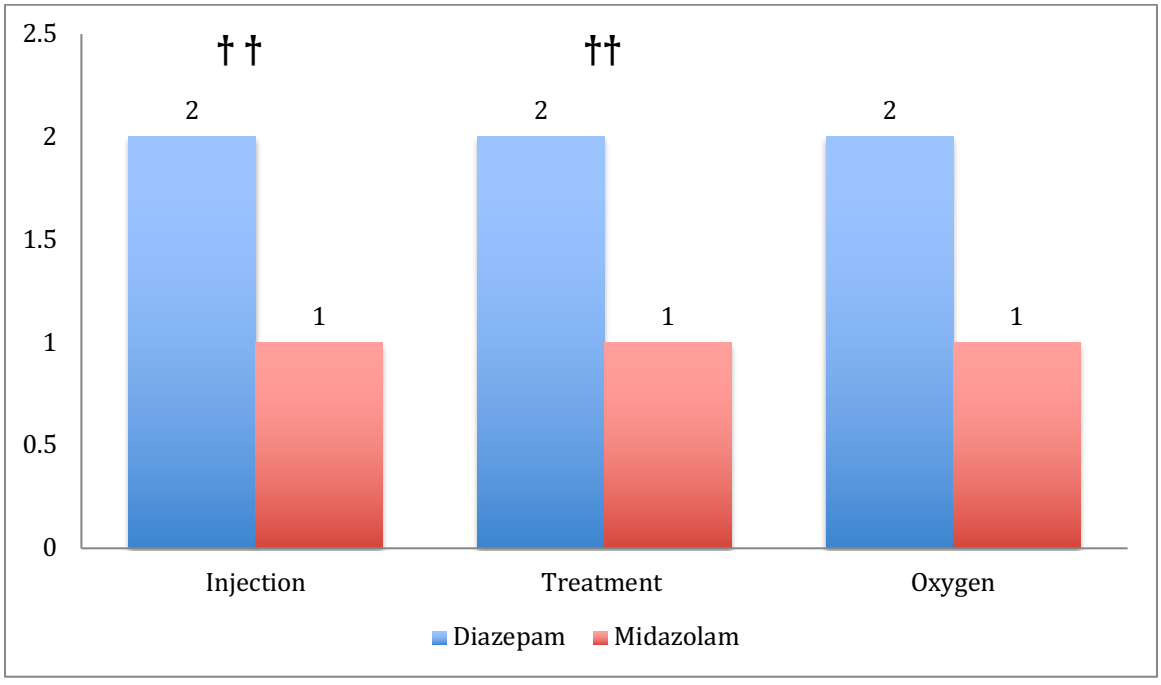
Figures

Figure 1: Median Frankl Score at Various Treatment Stages



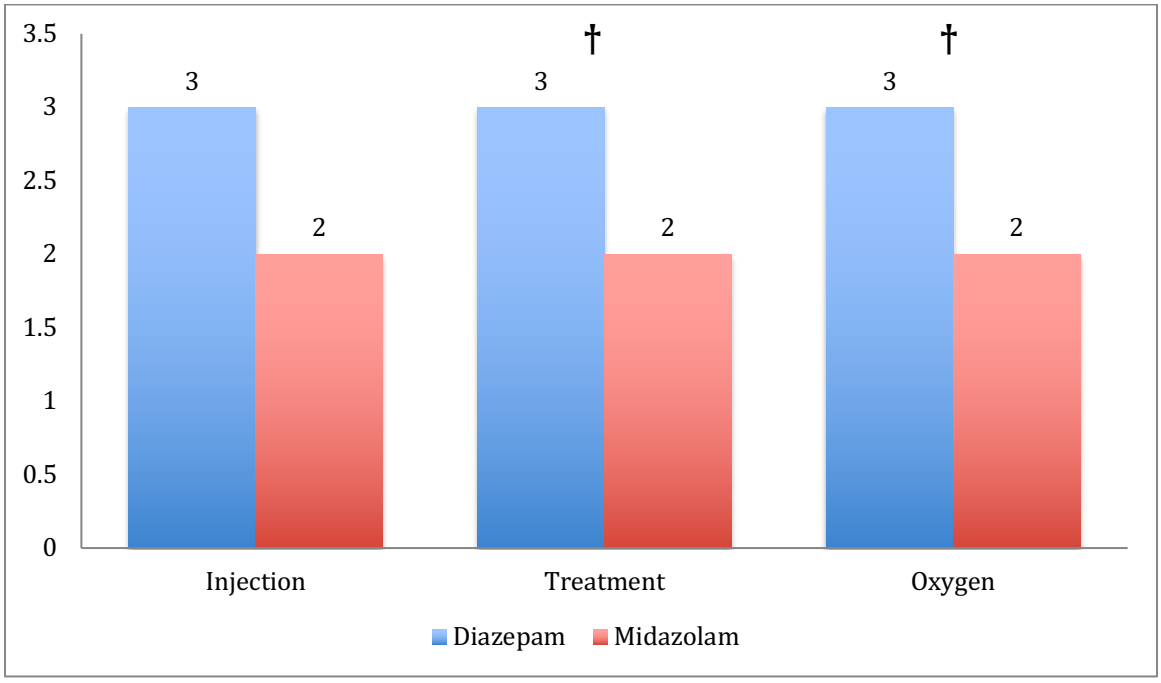
†Indicates significant difference at 0.10 level

Figure 2: Median Houpt Sleep Scores



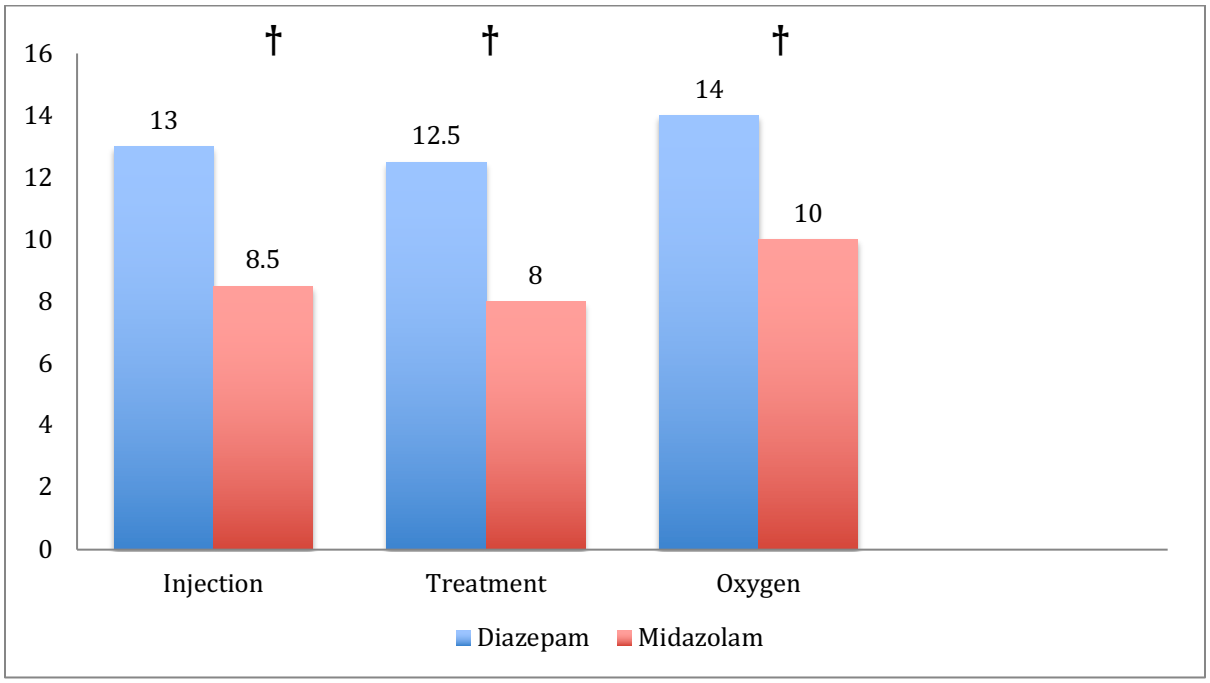
††Indicates significant difference at 0.05 level

Figure 3: Median Houpt Movement Scores at Various Treatment Stages



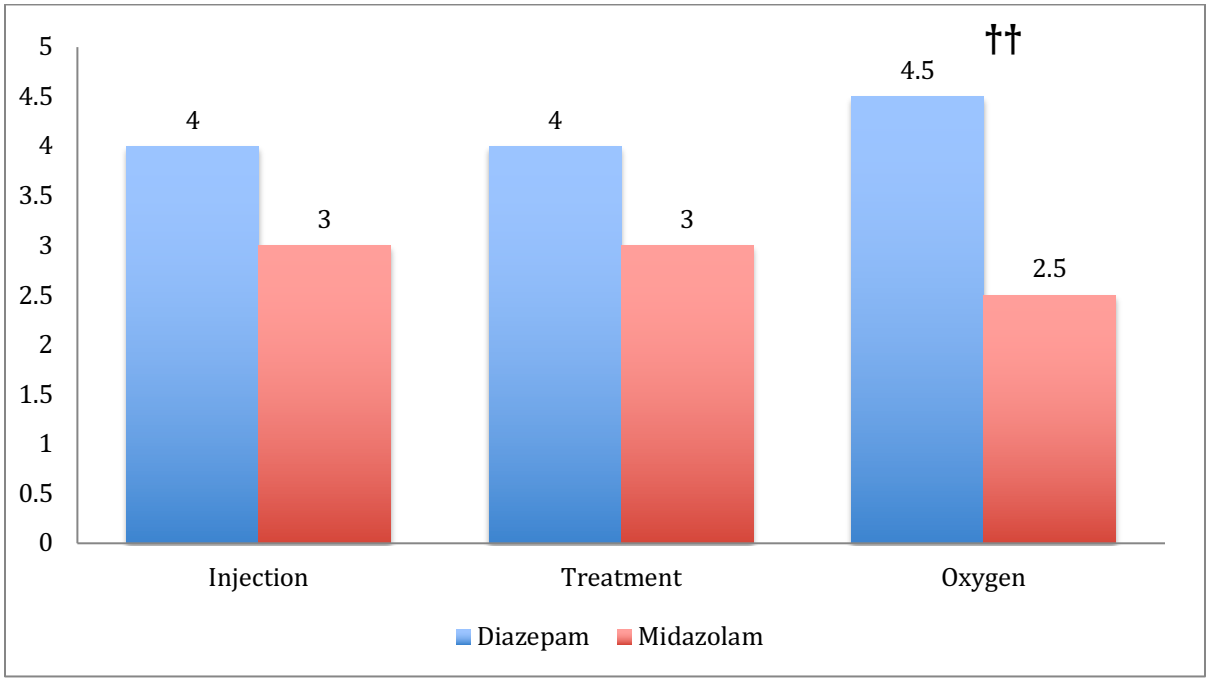
†Indicates significant difference at 0.10 level

Figure 4: Median Total Houpt Scores at Various Treatment Stages



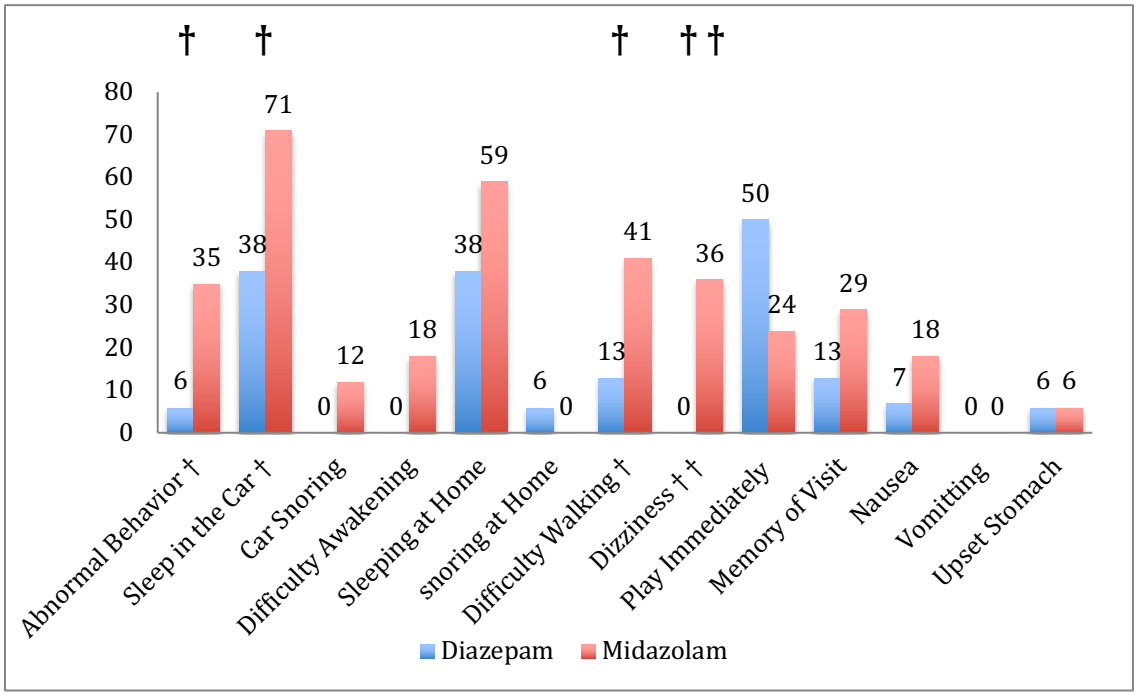
†Indicates significant difference at 0.10 level

Figure 5: Median Houpt Overall Behavior Score



††Indicates significant difference at 0.05 level

Figure 6: Guardian Reported Side Effects at 8 Hour Post Op Call



†Indicates significant difference at 0.10 level

Appendix

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 Rating 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: Monitor 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

Subject #:_____

OCS Date:_____

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?		
How long did they sleep 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?		

For PI Use Only:

Regimen:

Weight:
Hydroxyzine:
Demerol:
Diazepam:
Midazolam:

Procedures completed:
Anterior comp:_____
Posterior comp:_____
SSC:_____
Pulp therapy:_____
Extractions:_____
Miscellaneous: _____

References

1. Nelson T, Xu Z. Pediatric dental sedation: challenges and opportunities. *Clin Cosmet Investig Dent*. 2015;7:97.
2. 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.
3. McCormack L, Chen 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.
4. Huang A, Tanbonliong T. Oral Sedation Postdischarge Adverse Events in Pediatric Dental Patients. *Anesth Prog*. 2015;62(3):91-99.
5. Tyagi P, Tyagi S, Jain A. 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.
6. 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(5):417-424.
7. Lourenço-Matharu L, Ashley PF, Furness S. Sedation of children undergoing dental treatment. *Cochrane Database Syst Rev*. 2012;(3).
8. Young ER. Sedation: A Guide to Patient Management, 4th Edition. *Anesth Prog*. 2006;52(1):43-44.

9. Diazepam. [Package Insert]. Eatontown, NJ: Westward Pharmaceuticals Corp. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1aaf9375-ae3d-4fed-9cd1-24102e00be1a&audience=consumer. Published 2016. Accessed March 23, 2019.

10. Midazolam. [Package Insert]. Eatontown, NJ: Westward Pharmaceuticals Corp. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a833c24b-6dca-44d7-a0d6-20012fa1ea77&audience=professional. Published 2017. Accessed March 23, 2019.

11. Meperidine. [Package Insert]. Eatontown, NJ: Westward Pharmaceuticals Corp. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=15bc51a8-1e24-4d33-9a2f-05a41c29acf0. Published 2019. Accessed March 23, 2019.

12. Hydroxyzine. [Package Insert]. Philadelphia, PA: Lannett Company Inc. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a4fb61ae-aad6-4bd6-83fc-8b227f175df9. Published 2018. Accessed March 23, 2019.

13. Clark RF, Wei EM, Anderson P 0. Meperidine: Therapeutic Use and Toxicity. *J Emerg Med*. 1995;13(6):797-802.

14. Cote CJ, Wilson S, Coté CJ, Wilson S, Work Group on Sedation. Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures: An Update. *Pediatrics*. 2006;118(6):2587-2602.

15. Cote CJ, Lerman J, Ward R, Lugo RA, Goudsouzian N. Pharmacokinetics and Pharmacology of Drugs Used in Children: Chapter 6. In: *A Practice of Anesthesia for Infants and Children*. 4th ed. Philadephia, PA: Saunders Elsevier; 2009:pp: 89-146.

16. Gerlach M, Warnke A, Greenhill L. *Psychiatric Drugs in Children and Adolescents: Basic Pharmacology and Practical Applications*. (Gerlach M, Warnke A, Greenhill L, eds.). Springer; 2014.

17. Malamed SF. *Sedation: A Guide to Patient Management*. 6th ed. St. Louis, Missouri; 2018.

18. Griffin CE, Kaye AM, Bueno FR, Kaye AD, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J*. 2013;13(2):214-223.

19. Becker DE. Pharmacokinetic Considerations for Moderate and Deep Sedation. *Anesth Prog*. 2011;58:166-173.

20. Sdrales LM, Miller RD. *Miller's Anesthesia Review*. 3rd ed. (Sdrales LM, ed.). Philadephia, PA: Elsevier; 2018.

21. Da Settimo F, Taliani S, Trincavelli M, Montali M, Martini C. GABAA/Bz Receptor Subtypes as Targets for Selective Drugs. *Curr Med Chem*. 2007;14(25):2680-2701.

22. Friedman H, Abernethy DR, Greenblatt DJ, Shader RI. The pharmacokinetics of diazepam and desmethyldiazepam in rat brain and plasma. *Psychopharmacology (Berl)*. 1986;88(3):267-270.

23. Komur M, Arslankoylu AE, Okuyaz C. Midazolam-induced acute dystonia reversed by diazepam. *J Anaesthesiol Clin Pharmacol*. 2012;28(3):368-370.

24. Shin YH, Kim MH, Lee JJ, et al. The effect of midazolam dose and age on the paradoxical midazolam reaction in Korean pediatric patients. *Korean J Anesthesiol*. 2013;65(1):9-13.

25. Arai Y-CP, Fukunaga K, Hirota S. Comparison of a combination of midazolam and diazepam and midazolam alone as oral premedication on preanesthetic and emergence condition in children. *Acta Anaesthesiol Scand*. 2005;49(5):698-701.

26. Nathan JE, Vargas KG. Oral midazolam with and without meperidine for management of the difficult young pediatric dental patient: a retrospective study. *Pediatr Dent*. 2002;24(2):129-138.

27. Dosani FZ, Flaitz CM, Whitmire HCJ, Vance BJ, Hill JR. Postdischarge events occurring after pediatric sedation for dentistry. *Pediatr Dent*. 2014;36(5):411-416.

28. 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.

29. 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.

30. Patel M, McTigue DJ, Thikkurissy S, Fields HW. Parental Attitudes Toward Advanced Behavior Guidance Techniques Used in Pediatric Dentistry. *Pediatr Dent*. 2016;38(1):30-36.

31. 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.

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

33. Moura L da S, Costa PS, Costa LR. How Do Observational Scales Correlate the Ratings of Children's Behavior during Pediatric Procedural Sedation? *Biomed Res Int*. 2016;2016:5248271.

34. Parikh, Ojas A, Dahlke WO. A Comparison of Moderate Oral Sedation Drug Regimens for Pediatric Dental Treatment: A Pilot Study. *Viginia Commonw Univ VCU Sch Campus*. 2017.

35. AAPD. Monitoring and Management of Pediatric Patients Before, During, and After

Sedation for Diagnostic and Therapeutic Procedures: Update 2016. *Pediatr Dent Ref Man*. 2016;39(6):278-307.

36. 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.

37. Peretz B, Kharouba J, Somri M. A comparison of two different dosages of oral midazolam in the same pediatric dental patients. *Pediatr Dent*. 36(3):228-232.

38. Musial KM, Wilson S, Preisch J, Weaver J. Comparison of the Efficacy of Oral Midazolam Alone Versus Midazolam and Meperidine in the Pediatric Dental Patient. *Pediatr Dent*. 2003;25.