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Effect of moderate sedation regimen (diazepam, meperidine, and hydroxyzine) dosages on patient behavior and outcome of sedation in Pediatric Dentistry: a retrospective study

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

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Abstract

EFFECT OF MODERATE SEDATION REGIMEN (DIAZEPAM, MEPERIDINE, AND HYDROXYZINE) DOSAGES ON PATIENT BEHAVIOR AND OUTCOME OF SEDATION IN PEDIATRIC DENTISTRY: A RETROSPECTIVE STUDY

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Purpose: To determine if behavior at consult visit and sedation medication dosages are associated with the success of sedation visits and patient's behavior using the diazepam, meperidine, and hydroxyzine (DMH) regimen.

Methods: A retrospective chart review was conducted of 324 VCU Pediatric Dentistry Department patients who underwent 404 moderate conscious sedation visits with DMH regimen from April 2017 to June 2022. Sedation visits were graded as "Successful" or "Unsuccessful" and "Good" or "Poor behavior." The primary variables of interest included Frankl behavior at consult visit and the sedation medication dosages. Logistic regression models were used to determine if these factors were associated with sedation success and overall sedation behavior while adjusting for other patient and sedation characteristics.

Results: The regimen yielded mostly successful sedations (89%) and "Good Sedation Behavior" (Frankl 3 and 4) (72%). Lower Frankl scores at consult visits (OR: 2.3, P=0.0140) were associated with increased odds of failure. Increased age (OR: 0.8, P=0.0047) was associated with decreased odds of sedation failure. Meperidine dose demonstrated trends towards significant association with potential for clinical relevance.

Conclusion: This study shows that the diazepam, meperidine, and hydroxyzine (DMH) regimen is an effective moderate sedation regimen. Patient selection is a significant factor in the success of the DMH moderate sedation.

Introduction

Background

Moderate sedation is an advanced behavior guidance method that is commonly used in pediatric dentistry.[1] Many scenarios lead the pediatric dentist to elect for the sedation of pediatric patients when undergoing dental procedures. The American Academy of Pediatric Dentistry (AAPD) summarizes the indications for sedation as follows; fearful/anxious patients for whom basic behavior guidance techniques have not been successful; patients who cannot cooperate due to a lack of psychological or emotional maturity and/or mental, physical, or medical conditions; and patients for whom the use of sedation may protect the developing psyche and/or reduce medical risk.[1] The goal of sedation is to decrease the patient's movement during the appointment for safer and better-quality dental treatment, as well as, minimize any possible discomfort and pain.[1]

Moderate sedation is defined as "drug-induced depression of consciousness during which patients respond *purposefully* to verbal commands or after a light tactile stimulation."[2] During moderate sedation, patients should be able to maintain a patent airway, spontaneous ventilation, and cardiovascular function. Sedation has been used in the field of pediatric dentistry for many years. According to Project USAP (Use of Sedative Agents in Pediatric Dentistry) which

surveyed dentists in 1985 and was updated periodically through 2010, oral sedation was the most commonly used method (93%), and nitrous oxide and benzodiazepines are the most utilized sedation agents.[3] Parenting style changes during the last decade has provoked the desire for more options for treating pediatric patients in the dental setting without eliciting negative experiences.[4] Studies that examined parental acceptance and perception of pediatric dental sedation concluded that parents have become more accepting of moderate sedation and prefer that their children sleep throughout the entire procedure or be somewhat sleepy, rather than completely awake and alert.[4] In addition, another study that evaluated a Turkish population, found sedation to be preferred to general anesthesia or protective stabilization when different modalities of behavior management were presented.[5]

Successful sedations encourage a positive experience and reduce the possibility of negative traumatic experiences for the pediatric patient.[1] In a survey that investigated pediatric dentists and their perceived success of sedations when used with nitrous oxide, perception of sedation success was measured to be greater than 75%.[6] Therefore, many pediatric dentists prefer the use of sedation to enable the provision of optimal dental treatment. However, when sedation is not successful, providers manage events differently. A survey, that evaluated pediatric dentists, revealed that 68% of providers would resort to general anesthesia or other available options, if a certain sedation regimen failed, whereas, only 19% would actually try a different sedation regimen, or adjust the doses of the regimen that previously failed.[7] The subjectivity of managing unsuccessful sedations brings the question: does changing medication dosages for the same regimen provide any additional benefit for the non-cooperative sedated patient?

Despite the fact that conscious sedation is accepted and utilized by providers, there is a wide array of actual regimens and no particular gold standard. There is subjectivity in both

dosing and medications selected by pediatric dentists.[8] The triple regimen: diazepam, meperidine and hydroxyzine (DMH) has been used for many years by pediatric dentists to achieve moderate sedation. However, significant scarcity is noted in published literature that assesses the effectiveness of this regimen and no guidelines for particular dosing of the medications. Proving the validity and best practices of the DMH regimen in achieving predictable sedations can provide clinicians with more sedation options.

In a comparative retrospective study, when oral midazolam (Versed), was combined with meperidine, it showed that achieving successful sedation improved significantly, while it led to increased depth of sedation.[9] Combination of midazolam with meperidine dosing ranges 0.7-1.0 mg/kg and 1.0-1.5 mg/kg, respectively, were preferred as they allowed for the most predictable sedations in terms of ability to complete treatment, safety, and depth of sedation.[9] Literature review did not yield any similar studies for the DMH regimen, further proving the need for more research in the realm of consistency of medication dosages and its associated outcomes.

The triple combination of oral sedation medications, diazepam, meperidine and hydroxyzine has shown promising results as it helps alleviate anxiety and reaches a usually predictable level of sedation enabling pediatric dentists to provide quality treatment.[10] A previous study conducted at VCU Pediatric Dentistry Clinic measured the effectiveness of diazepam, meperidine and hydroxyzine (DMH) combination drug therapy, in comparison to midazolam, meperidine, and hydroxyzine (MMH) sedation regimen. It showed DMH regimen to be more effective in achieving less failed sedations (30% vs. 55%); although the results did not reach statistical significance, they were clinically relevant.[10] When a follow-up phone call survey was conducted post-operatively, DMH was found to have slightly more side effects post-operatively, most notably increased sleeping time in the car on the way home following the

appointment. However, patients treated with MMH experienced more dizziness, complained more and had issues walking. The study concluded that the DMH triple combination sedation regimen shows promising results as a successful alternative to midazolam triple combination. However, longer postoperative monitoring may be required with diazepam.[10]

Risks and Pharmacology of Sedation Drugs

Different sedation regimens by the oral route exist and have been utilized for many years. Several updates and advances in pharmacology and science contribute to continuous changes in moderate sedation and the preferred medications, their applications and administration, as well as the availability of reversal agents for these medications. Sedation medications, especially in pediatrics, are selected for their margin of safety and overall effectiveness while using the most minimal dose possible.[2] Some factors play a significant role in pediatric dentistry sedation; including sedation medications and their dosages, extent of dental treatment needed, patient's age, temperament and behavior, as well as personality traits.[11]

Moderate sedation is considered an advanced behavior management technique associated with some risks. Some critical risks related to sedation can be brain damage; and in rare cases, death, mostly due to a compromised airway that decreases oxygen delivery to the brain and/or cardiovascular effects, where the heart is unable to compensate for shifts in normal body systemic functions. Other possible but not life-threatening risks can be nausea and vomiting, prolonged sedation, as well as paradoxical reaction.[12]

Benzodiazepines, specifically diazepam (Valium), are widely used for their anti-anxiety, anti-convulsant, sedative, hypnotic and anterograde amnesic properties, as well as for providing some musculoskeletal relaxation. Benzodiazepines potentiate GABA receptors producing their

sedative effects, acting mainly on the central nervous system and with minimal effects on the cardiovascular system and breathing function when used alone.[13] In a Cochrane review, oral diazepam by itself did not improve behavior when compared to placebo.[14] Flumazenil (Romazicon) is an available reversal agent for benzodiazepines that adds to the safety of diazepam.[15]

Meperidine (Demerol) works as an agonist to μ(mu)-opioid receptors producing analgesia. Meperidine is a narcotic agent, causing the most sedation with slight analgesia by acting on the central nervous system; however, it also causes depression of the cardiovascular and respiratory systems and has a narrow therapeutic index.[16,17] When meperidine is combined with other sedatives it can result in profound sedation and increased depression of systemic functions.[16] In rare instances, an allergic phenomenon can develop as the body reacts to opioids by releasing histamines, sometimes presenting as urticaria and skin rashes.[13] Therefore, some contraindications to meperidine include sensitivity to morphine or other narcotic agents, and moderate to severe asthma.[16] Another possible adverse reaction to meperidine is seizures as this drug can lower the seizure threshold for patients.[18] A Cochrane review found that meperidine, as a single agent, shows improved patient behavior.[14] Naloxone (NARCAN) is a reversal agent for meperidine if an overdose or an adverse reaction is suspected.[19]

Lastly, hydroxyzine (Vistaril) has an established use as an anti-anxiety medication and at certain doses can cause marked sedation, potentiating the sedative effects of meperidine while counteracting the histamine release.[13] Hydroxyzine is also beneficial as it causes airway musculature relaxation and acts as a bronchodilator. Additionally, it has an antiemetic effect, counteracting the possible side effects of using a narcotic agent such as meperidine. Moreover, a side effect of histamine receptor antagonists is the mild anticholinergic and antisecretory

activity,[20] which proves to be beneficial when working in the oral environment to lower the risk of contamination and risk of aspiration while the patient is sedated. The Cochrane review showed that no certain dose was deemed more effective and disagreement with hydroxyzine dosing was noted.[14]

Sedation and Impact on Behavior Management

The AAPD categorizes sedation as an advanced behavior guidance technique along with protective stabilization and general anesthesia. These advanced techniques require the provider to have proper additional training in managing patients for whom traditional behavior management techniques have failed.[1] Moreover, one of the objectives of sedation according to the AAPD is to manage the patient's behavior, minimize the psychological trauma while guarding the patient's safety.[1] A majority of published literature on behavior management techniques in pediatric dentistry is limited and of lower-quality evidence (opinion and survey papers); and the need for more predictable outcomes of behavior management and provision of dental care is an ongoing topic in pediatric dentistry.[21] Patient's anxiety and cooperation in pediatric dentistry is strongly correlated to their age, previous traumatic medical or dental experiences, or even the parent's own anxiety towards suggested therapy. All of the previous factors are important considerations in assessing if the child would undergo a successful sedation or if other treatment modalities are best to be utilized such as completing the dental treatment under general anesthesia.[22] Several studies have demonstrated that patients who take sedation medication willingly have more favorable outcomes.[23-25] Another trait that can predict behavior during sedation appointments is the impulsive behavior of the pediatric patient.[26]

Assessment of patient's behavior can be subjectively measured by using the Frankl Behavior Rating Scale (FBRS) that rates the patient's behavior from 1 to 4 (definitely negative, negative, positive and definitely positive, respectively).[27] Frankl behavior scale was introduced in 1962 is considered to be the most commonly used when documenting pediatric patients' temperament at pediatric dental office visits (Table 1).[1,27]

Table 1. Frankl Behavior Rating Scale (Adopted from AAPD's Behavior Guidance for the Pediatric Dental Patient)[1]

Frankl Behavior Rating Scale		
1	−−	Definitely negative. Refusal of treatment, forceful crying, fearfulness, or any other overt evidence of extreme negativism
2	−	Negative. Reluctance to accept treatment, uncooperative, some evidence of negative attitude but not pronounced (sullen, withdrawn)
3	+	Positive. Acceptance of treatment, cautious behavior at times, willingness to comply with the dentist, at times with reservation, but patient follows the dentist's directions cooperatively
4	++	Definitely positive. Good rapport with the dentist, interest in dental procedures, laughter and enjoyment

A questionnaire that queried pediatric dentists' definition of success in regards to sedations and the utilization of restraints whether passive or active found that close to 50% of pediatric dentists prefer to use sedation techniques over restraints.[28] In the same study, 47% of pediatrics dentists viewed the sedation as successful when behavior allowed completion of treatment despite using forms of immobilization, whereas 49% believed that if the use of restraint allowed completion of sedation treatment and avoiding general anesthesia, it deemed the sedation as acceptable. However, general disagreement is noted in different practitioners' definition of a successful sedation; some would classify any completion of work under sedation as successful whereas some consider only better behavior during sedation as successful.[28]

Purpose of the study

Pediatric dentists assess behavior on a routine basis for every patient to predict the best environment to deliver quality and safe dental therapy. Clinicians may predict the possibility of success of sedation based on patient behavior at previous visits. However, this prediction is merely subjective and mostly based on the provider's clinical experience. Providers also rely on experience and training when considering preferred dosages of oral sedation medications.[7] Providers lack clear, evidence-based guidance on both medication dosages and patient selection for moderate sedation.

The purpose of this study was to assess the overall success of the diazepam, meperidine, and hydroxyzine (DMH) moderate sedation of pediatric patients in the dental setting. Additionally, this study focused on the effect of patient selection and medication dosages on sedation success and patient behavior during sedation.

Methods

Study Design: This study was a retrospective chart review of Virginia Commonwealth University - Pediatric Dentistry Department Clinic patients who underwent moderate sedation using triple regimen with diazepam, meperidine, and hydroxyzine. This study was approved as exempt by the Institutional Review Board at Virginia Commonwealth University (IRB: HM20021080)

Data collection: Data was collected from patients' charts who underwent oral moderate sedation with the diazepam, meperidine and hydroxyzine moderate sedation at Virginia Commonwealth University - Pediatric Dental Clinic (Richmond, VA. USA) during the period (June 2017-April 2022). Dental records were obtained from axiUm software (Deltek Inc., 2022) of all patients who underwent Non-Intravenous Conscious Sedation (CDT code: D9248). All patients who received another drug regimen were excluded. Two reviewers, one primary reviewer and another secondary reviewer, collected data from dental records and variables were entered into a separate electronic secure database. Variables recorded from dental records were as follows: gender, age at time of treatment, date of procedure, treatment completed, extraction vs. no extraction, Frankl scoring for both sedation and previous consult visit (when two Frankl scores were given for visits, primary reviewer evaluated sedation record sheets and predominant behavior rating was entered into the dataset), provider year in residency (R1 or R2), and any complications during

treatment, as well as, if aborted treatment resulted in a general anesthesia referral. Sedation monitoring records (adopted from the AAPD guidelines for sedation monitoring) were scanned into patients' charts and accessed via attachments in axiUm where the following variables were collected: patient's weight on the day of the sedation, dosages of sedation medications (diazepam, meperidine, and hydroxyzine), fasting (NPO) status, sedation level (none, minimal, moderate, deep, general anesthesia), and sedation behavior (excellent, good, fair, poor, prohibitive). When weight at day of the procedure was not recorded, the closest weight to the sedation visit was recorded with a maximum of 30 days prior to sedation visit.

Inclusion criteria and sedation protocol at VCU Pediatric Dental Clinic

All patients who underwent diazepam, meperidine, and hydroxyzine triple regimen sedation at VCU Pediatric Dentistry Department administered by residents with the supervision of full-time and part-time faculty regardless of age and weight were included in the study from April 2017 to June 2022.

VCU Pediatric Dentistry Clinic sedation protocol follows the AAPD guidelines. All included patients were ASA I and ASA II to qualify for in-office sedation. All patients met the NPO criteria as indicated by the AAPD guidelines.[2] A recent history and physical for the patient that clears health status to allow completion of in-office moderate sedation is reviewed prior to sedation. Prior to administering oral sedation medication at day of sedation, patient's weight, history of recent illness, NPO status, Brodsky score, blood pressure, oxygen saturation, as well as, breath and heart sounds were examined and recorded to ensure the optimal health of the patient. Standard of care at VCU Pediatric Dental Clinic is to complement sedation medications

with nitrous oxide and to consent guardians for the possible use of immobilization if needed. The use of nitrous oxide inhalation and immobilization were not collected as part of this study.

Exclusion criteria

Any patient with special health care needs that might cause barriers in communication, such as an official medical diagnosis of autism spectrum disorder or developmental delay, as well as data records that had inadequate information were excluded from this study. As this is a retrospective study, ineligible cases and patients who did not meet the moderate sedation criteria were excluded beforehand; therefore, these criteria are not discussed in this thesis.

Available medication in VCU Pediatric Dentistry Clinic

Medications used in this regimen were as follows:

1. Diazepam: dispensed in 5mg tablets, or as concentrate oral solution (Intensol™) and
2. Meperidine Hydrochloride: dispensed as oral solution (50mg/5ml) and
3. Hydroxyzine Hydrochloride: dispensed as 10 mg tablets and 25 mg tablets or
4. Hydroxyzine Pamoate: dispensed as 25 mg capsule

Behavior assessment using Frankl Behavior Rating Scale (FBRS)

In this study, Frankl Behavior Rating Scale was used to assess patient cooperation level and the behavioral component of the sedation procedure. Frankl scores of sedation consult appointments were also collected to compare to Frankl scores during sedation appointments.[1,27]

Evaluation of sedation success/failure

Successful Sedation was defined as the ability to complete proposed treatment exactly as planned or with differences in suggested treatment plan as long as any definitive treatment was completed. Placement of hall crowns was considered as "Successful."

Unsuccessful Sedation was defined as any sedation visit that no treatment was completed or planned treatment was aborted and only temporary treatment (placement of sedative filling, application of Silver Diamine Fluoride, etc.) could be rendered.

Evaluation of patient behavior during sedation

Poor Sedation Behavior was defined as any unfavorable or negative outcome of the sedation visit, and measured as sedation visits that scored Frankl 1 or 2.

Good Sedation Behavior was defined as any favorable or positive outcome of the sedation visit, and measured as sedation visits that scored Frankl 3 or 4.

Statistical methods

Frankl scores during the sedation visit and at the consult appointment were compared using Wilcoxon signed-rank test. Spearman correlation coefficient was used to evaluate the bivariate association between the medication dosage and the Frankl score. Kruskal-Wallis test was used to test for differences in the average dose of each medication based on the Frankl scores. Logistic regression models were used to evaluate the effect of medication dosages, age,

gender, consult appointment Frankl score, and the number of sedation visits the child has had on the probability of a successful treatment and patient behavior during sedation visit. To determine if inclusion of subsequent sedation visits from same patients biased associations with sedation success or sedation behavior, sensitivity analyses were performed with only the first visit for each patient. Significance level was set at 0.05. SAS EG v.8.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

Characteristics of dataset

Data from 404 patient sedations and 324 patients were used for the analysis. The average age (at first sedation) was 6.8 (SD=2.5) and ranged from 0 to 17. About half (52%, n=170) were female. Second year residents were the provider for 70% of the cases. The average doses of the triple combination medications were within recommended dosing ranges and are presented in Table 2 along with other characteristics of the sedation visits in Table 3. For diazepam, the average dose was 0.28 mg/kg and ranged from 0.12-0.74 mg/kg. For meperidine, the average was 1.9mg/kg and ranged from 0.6-2.9 mg/kg. For hydroxyzine, the average dose was 1.5 mg/kg and ranged from 0.51-3.15 mg/kg.

Table 2. Average age and medication dosages for all sedation visits (n=404)

	Mean	SD
Age	6.85	2.31
Medication Dosages (mg/kg)		
Diazepam	0.28	0.05
Meperidine	1.89	0.43
Hydroxyzine	1.53	0.48

Table 3. Summary of patient and sedation visit characteristics for all sedation visits (n=404)

	Total (n)	Percentage (%)
Gender		
Female	214	53%
Male	190	47%
Result		
Successful	361	89%
Unsuccessful/Failure	43	11%
Frankl Score at consult visit		
1	17	4%
2	81	20%
3	229	57%
4	76	19%
Frankl Score at sedation visit		
1	62	15%
2	54	13%
3	136	34%
4	152	38%
Extraction visits	159	39%
Number of sedation visits		
1	324	80%
2	70	17%
3+	10	2%
Provider Experience		
R1	123	30%
R2	281	70%
Referred to General Anesthesia	42	10%

The majority of sedation visits were successful (89%) in allowing completion of all or some definitive treatment. Failed sedations accounted for the remaining 11% of sedations. Of these failures, 70% were referred to general anesthesia to complete treatment. Overall, 10% of sedation visits were referred to general anesthesia, including some patients with what was

considered successful sedation. Referral to general anesthesia can be due to many other factors, for example when the sedation was successful but radiographs obtained on the day of sedation revealed more extensive lesions than originally planned, and visits that only allowed completion of some treatment. In terms of patient behavior, not by provision of definitive treatment, 71% were considered "Good Sedation Behavior" based on the Frankl scores (3 or 4) and 29% were considered "Poor Sedation Behavior" Based on Frankl scores (1 or 2).

The median Frankl score was 3 for both the consult visit and the sedation visit. Results from Wilcoxon signed-rank test indicated the Frankl score during the sedation was not significantly different from the work-up visit (p-value=0.5313). The median difference between the two visits was 0 with an interquartile range of -1 to 1.

Behavior at consult visits was significantly associated with Frankl score at sedation visit (p-value <0.0001). Those with lower Frankl scores at consult (F1, F2), had greater proportion of "Poor Sedation Behavior" during the sedation. In contrast, those with higher Frankl scores at consult had a greater proportion of "Good Sedation Behavior." This relationship is displayed in Figure 1.

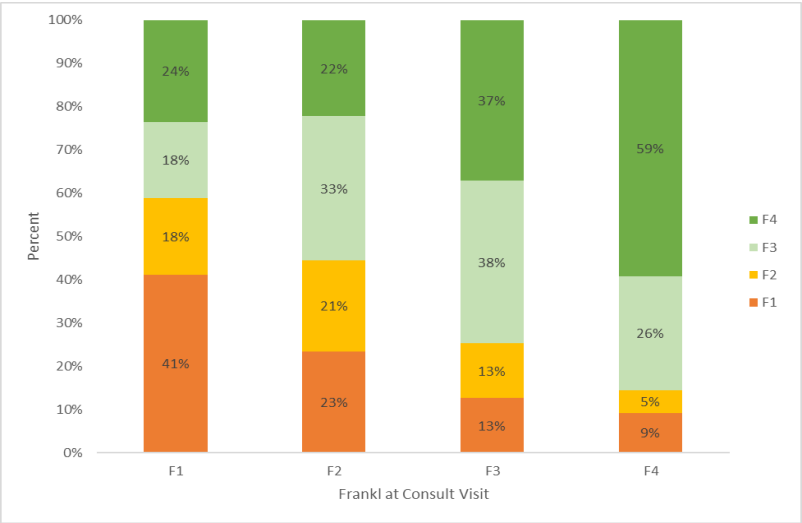


Figure 1. Distribution of Sedation Visit Frankl Scores by Frankl Score at Consult Visit

Based on bivariate associations, dosage values for the medications in the triple combination were not significantly associated with the sedation visit Frankl scores (Figures 2-4). The Spearman correlation coefficients were 0.03 (p=0.5274) for meperidine, -0.06 (p=0.2214) for diazepam, and -0.01 (p=0.9130) for hydroxyzine. Kruskal-Wallis tests for differences in dosage based on the Frankl scores were also not statistically significant for any of the three medications (p-values>0.2758).

Figure 2. Diazepam Dosage Distribution by Frankl Score

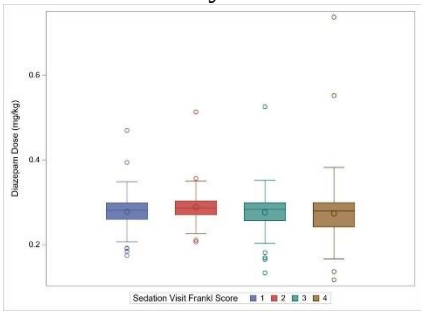


Figure 3. Meperidine Dosage Distribution by Frankl Score

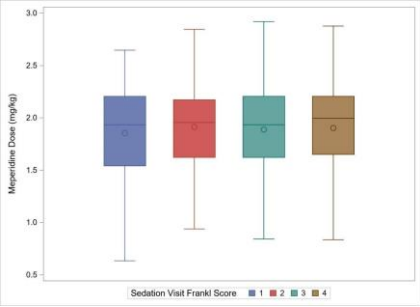
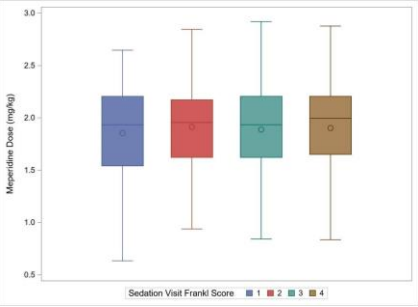


Figure 4. Hydroxyzine Dosage Distribution by Frankl Score



Extractions Data Analysis

Extractions were analyzed to compare against Frankl scores to determine if the complex nature of extractions was related to sedation behavior. Frankl scores during sedation were significantly associated with whether or not extractions were performed (p-value=0.0018). However, cases with extractions were actually found to have a higher rate of “Good Sedation Behavior” (Frankl 3 or 4) with 77% Frankl 3 or 4 compared to 68% of cases without extractions (Table 4).

Table 4. Extractions associated with Frankl score at sedation visit

Frankl	Extractions	No Extraction
1	14 (9%)	49 (20%)
2	23 (14%)	31 (13%)
3	68 (43%)	68 (28%)
4	55 (34%)	97 (40%)

Factors Associated with Successful Treatment (All Sedations)

Based on the multivariable logistic regression, successful treatment was associated with age (p=0.0047), and Frankl score at the consult appointment (p =0.0140). A 1-year increase in age was associated with a decrease of 0.8 times odds of failure (95% CI: 0.64-0.92). Patients with a Frankl score of 1 or 2 at the consult visit were 2.3 times as likely to have a failed sedation than those with a Frankl of 3 or 4 at the consult (95% CI: 1.19-4.60). There was a trend towards significant association between meperidine dose and sedation success (p-value=0.0557). As meperidine dose increased, the odds of failure decreased (OR: 0.9; 95% CI: 0.84-1.00). Model results are presented in Table 5.

Table 5. Multivariable Logistic Regression Model of Sedation Failure for all sedation visits (n=404)

	Adjusted Odds Ratio (Odds of Failure)	**95% CI**	**p-value**
Age	0.8	0.64-0.92	0.0047*
Gender (Female vs Male)	0.9	0.46-1.67	0.6843
Triple Dose (0.1mg/kg increase)			
Diazepam	1.1	0.64-1.96	0.6809
Meperidine	0.9	0.84-1	0.0557
Hydroxyzine	1.0	0.93-1.08	0.8875
Sedation Number	0.7	0.33-1.54	0.3861
Consult Frankl Score (1-2 vs 3-4)	2.30	1.19-4.6	0.0140*

***P<0.05**

Factors Associated with Successful Treatment (First Sedations Only)

When considering only patients' first sedation visits, there were a total of 324 sedations with a success rate of 89% (n=287/324). Based on multivariable logistic regression, successful treatment on the first sedation visit was associated with age (p=0.0028), Frankl score at the consult appointment (p =0.0361), and meperidine dose (p=0.0240). A 1-year increase in age was associated with decrease of odds of failure with an odds ratio of 0.8 times (95% CI: 0.69-0.95). Patients with a Frankl score of 1 or 2 at the consult visit were 2.2 times as likely to have a failed sedation than those with a Frankl of 3 or 4 at the consult (95% CI: 1.05-4.68). A 0.1mg/kg

increase in meperidine was associated with a decreased odds of failure with an odds ratio of 0.9 times (95% CI: 0.81-0.99). Model results are presented in Table 6.

Table 6. Multivariable Logistic Regression Model of Sedation Failure for first visits only (n=324)

	Adjusted Odds Ratio (Odds of Failure)	**95% CI**	**p-value**
Age	0.7	0.61-0.9	0.0028*
Gender (Female vs Male)	0.9	0.45-1.83	0.7742
Triple Dose (0.1mg/kg increase)			
Diazepam	1.0	0.58-1.86	0.8905
Meperidine	0.9	0.81-0.99	0.0240*
Hydroxyzine	1.0	0.93-1.1	0.7828
Consult Frankl Score (1-2 vs 3-4)	2.2	1.05-4.68	0.0361*

***P<0.05**

Factors Associated with Sedation Behavior (All Sedations)

Of the 404 sedations, 116 (29%) would be considered "Poor Sedation Behavior" based on a Frankl of 1 or 2. These cases include the 10% of cases that were considered failures along with other difficult sedation visits. Based on multivariable analysis, "Poor Sedation Behavior" was associated with patient age ($p<0.0001$), consult visit Frankl ($p<0.0001$), and meperidine dose ($p=0.0178$). A 1-year increase in age was associated with a decreased odds of "Poor Sedation Behavior" of 0.8 times (95% CI: 0.7-0.9). Patients with a consult Frankl score of 1 or 2 were 3.3 times more likely to have "Poor Sedation Behavior" (95% CI: 2.0-5.5). A 0.1 mg/kg increase in meperidine dose was associated with a decreased odds of "Poor Sedation Behavior" of 0.9 times (95% CI: 0.9-1.0). There was also a marginally significant association between "Poor Sedation Behavior" and subsequent sedation visits ($p=0.0666$). Each additional sedation was associated

with 0.6 times the odds of being considered a “Poor Sedation Behavior” (95% CI: 0.35-1.04). Complete results are displayed in Table 7.

Table 7. Multivariable Logistic Regression Model of Sedation Behavior for all sedation visits (n=404)

	Adjusted Odds Ratio (Odds of Poor Behavior)	**95% CI**	**p-value**
Age	0.8	0.69-0.88	<0.0001*
Gender (Female vs Male)	0.7	0.43-1.09	0.1070
Triple Dose (0.1mg/kg increase)			
Diazepam	1.3	0.79-1.97	0.3359
Meperidine	0.9	0.87-0.99	0.0178*
Hydroxyzine	1	0.94-1.05	0.7935
Sedation Number	0.6	0.35-1.04	0.0666
Consult Frankl Score (1-2 vs 3-4)	3.30	2.02-5.53	<0.0001*

***P<0.05**

Factors Associated with Sedation Behavior (First Sedations Only)

When considering only patients’ first sedation visits, similar trends were observed. Again, “Poor Sedation Behavior” was significantly associated with patient age (p<0.0001), consult Frankl score (p<0.0001), and meperidine dose (p=0.0255). A 1-year increase in age was associated with a decreased odds of “Poor Sedation Behavior” of 0.8 times (95% CI: 0.7-0.9). Patients with a consult Frankl score of 1 or 2 were 3.6 times more likely to have “Poor Sedation Behavior” (95% CI: 2.1-6.3). A 0.1 mg/kg increase in meperidine dose was associated with a decreased odds of “Poor Sedation Behavior” of 0.9 times (95% CI: 0.9-1.0) (Table 8).

Table 8. Multivariable Logistic Regression Model of Sedation Behavior for first visits only (n=324)

	Adjusted Odds Ratio (Odds of Poor Behavior)	**95% CI**	**p-value**
Age	0.8	0.66-0.86	<0.0001*
Gender (Female vs Male)	0.7	0.41-1.14	0.1455
Triple Dose (0.1mg/kg increase)			
Diazepam	1.2	0.74-1.9	0.4802
Meperidine	0.9	0.86-0.99	0.0255*
Hydroxyzine	1.0	0.93-1.05	0.6620
Consult Frankl Score (1-2 vs 3-4)	3.6	2.05-6.31	<0.0001*

***P<0.05**

Discussion

Moderate sedation is an advanced behavior management technique endorsed by the American Academy of Pediatric Dentistry and governed by guidelines to ensure the safety and wellbeing of the pediatric patient.[1] A commonly used regimen for moderate sedation in pediatric dentistry is midazolam, meperidine, and hydroxyzine (MMH). In a study conducted at VCU Pediatric Dental Clinic, when the MMH triple was compared to the DMH regimen, it was perceived that the DMH regimen showed significantly more successful sedations. Therefore, it may be preferred by providers as it increased intraoperative sedation.[10] Characteristics of midazolam include shorter working time,[9] due to it being 1.5-2.5 times more potent than diazepam[29] and frequency of paradoxical reaction.[30] Adverse reactions to midazolam such as paradoxical effects that range from tachycardia, inconsolable crying, restlessness with agitation, dysphoria, and disorientation, hostility, as well as aggression and rage (sometimes also termed "benzodiazepine-induced disinhibition"), were recorded in various clinical trials, case reports and other studies.[29,30] For many years, VCU Pediatric Dental Clinic has been using the diazepam, meperidine, and hydroxyzine triple as the standard sedation medication combination, along with the routine use of nitrous oxide inhalation.[10] Successful sedations were subjectively very common with minimal complications. In spite of the fact that many studies in literature examine moderate sedation in pediatric dentistry, a very limited number of them discuss the diazepam, meperidine and hydroxyzine regimen in terms of effectiveness, safety, and preference. This

study aims to augment the established literature in evaluating medication dosages and patient behavior in response to the triple regimen DMH.

The overall success rate in our study is 89%, where success was measured as completion of any definitive dental treatment during the sedation visit. No published data for the triple DMH is present to compare results and draw conclusions. In general, perceived rate of success for moderate sedation was estimated to be higher than 75%, when a survey queried pediatric dentists based on their experience.[6] In one study where meperidine was added to midazolam the success of the sedation increased from 60% to 80%-94% (increased success rate with increased meperidine dose). The previous study concluded that the addition of meperidine improves sedation success when compared to midazolam sedation only. The DMH regimen has a high success rate, which can possibly be attributed to meperidine and its synergistic effects when added to benzodiazepines such as diazepam.[31]

In this study, the average age of first sedation visit in this study was 6.8, with 6 years (n=76) and 7 years of age (n=79) being the most frequent age sedated in office. In the Commonwealth of Virginia,[32] the age limit to qualify for dental treatment under general anesthesia is age 5 for patients with governmental insurance (Medicaid) which constitutes the majority of VCU Pediatric Dentistry patient population. Patients older than 5 years with lower levels of cooperation who are unable to be treated under general anesthesia due to insurance coverage may be more likely to experience failures and poor outcomes with sedation. Other studies report the mean age at sedation visits was often around 5 years of age,[23] in comparison to the result of our study, which found the mean age to be higher. This result can be one of the contributing factors to a higher rate of successful sedations with “Good Sedation Behavior” found in data as increased age is significantly associated with decreased sedation failure. VCU

Pediatric Dentistry is only one of two pediatric dentistry residencies in the Commonwealth of Virginia, and is often a last resort for patients who have had failed restorative visits in other offices but are ineligible for general anesthesia. In the university clinic, many of the referrals for sedations indicated pediatric patients requiring extensive dental work who had failed previous visits with outside dentists. These prior experiences could be traumatic for the patient, further increasing the chances of "Poor Sedation Behavior" and sedation failure.

Age yielded statistical significance in terms of sedation success, with an increase in age demonstrating a reduction in odds for a "Poor Sedation Behavior" outcome. Our study is consistent with the published results of another retrospective study as younger patients (3-4 years) had more odds of producing a failed sedation appointment.[23] Additionally, a trial study also concluded that the effects of meperidine sedations are more evident on older preschoolers.[33]

Project USAP that queried pediatric dentists showed oral sedation to be the most preferred route by majority of respondents to administer medications compared to other modalities.[34] According to this survey, most sedations were completed with diazepam and nitrous; however, the triple regimen discussed in this study (diazepam, meperidine, and hydroxyzine) was not accounted for in the published study. Moreover, there is a lack of consistency with dosing the DMH regimen as many providers have their own preferred dosing ranges based on their experience and comfort level with the sedation medications and handling depth of sedation.[34]

Diazepam has been extensively used in the dental field to alleviate anxiety.[34] This research finds the average dose of diazepam to be close to 0.3 (0.28) mg/kg when utilized in the triple regimen, which proved to be not statistically significantly associated with the success and failure of sedations. VCU Pediatric Dentistry Clinic sedation protocol lists 0.3 mg/kg and 10 mg

in total to be a maximum dose administered. Project USAP reported 358 respondents out of 1,642 using diazepam as a single agent or in combination. Majority of respondents (75%) reported using a dose of 0.3-0.5 mg/kg, whereas only 10% reported using a dose of 0.6-0.75 mg/kg, and the remaining reported using doses higher than 0.75 mg/kg.[34] Therefore, the average dose of diazepam used as part of the DMH regimen agrees with literature in terms of preferred dosing ranges.

In the current study, the average dose for meperidine was 1.9 mg/kg with a range of 0.6-2.9mg/kg. The wide range in dose may be a factor of provider preference and experience, as well as indicated by patient behavior and needs. Particularly low doses may be a result of patients with higher bodyweight that can reduce the dose (mg/kg) after reaching the recommended maximum dose of (50mg) by VCU Pediatric Dental Clinic protocol. Cases with more difficult procedures, including extractions where additional analgesia is beneficial, may have also utilized higher doses of meperidine. The results from this study noted statistically significant associations between meperidine dose and sedation failure for first sedation visits and with "Poor Sedation Behavior" for the subset of first visit and all sedation visits. Although meperidine dosage did not achieve statistical significance in terms of sedation success when considering all sedation visits, the magnitude of the relationship was the same for all four analyses (OR=0.9), with the greatest impact noted in the first sedation visit analysis. This can be due to the introduction of bias when analyzing subsequent sedation visits, as only patients who have had successful first sedations will receive a subsequent sedation visit.

Meperidine was third in popularity after diazepam and midazolam with 449 of survey answers reporting utilizing this medication in office sedations.[34] Variable dosing ranges can be noticed with 56% of respondents choosing 2 mg/kg as their default dose, 28% preferred 1 mg/kg,

and 9% chose a dose range as low as 0.3-0.5 mg/kg.[35] The majority of providers in the previous survey preferred dosage agrees with the average dose found in our study. One research showed that for the severely anxious patients even the addition of meperidine when combined with midazolam did not significantly increase the success of sedation (36%), while for the mildly and moderately anxious the success rates was 65-75% and 80-86%, respectively.[9] It is important to note that in the study, when the dose of meperidine with midazolam was increased to 1.5 mg/kg, the success for the moderately anxious increased up to 94%, which appeared to be statistically significant.[9] In another study that compared different intramuscular (IM) meperidine dosing ranges, significant effects on patient behavior were evident with increased dosages when compared to placebo.[33] Therefore, this can support our results that demonstrated possible clinical relevance of an association between increased meperidine dose and sedation visit outcomes (success and behavior) when taking into account other patient characteristics (age and behavior at consult visit).

Hydroxyzine is the second most utilized drug in dental pediatric sedations after midazolam with 470 respondents reporting its use in their sedations.[34] The average dose in the present study was 1.5 mg/kg, with a maximum recommended dose of (50 mg) as indicated by VCU Pediatric Dental Clinic protocol. Hydroxyzine showed the greatest variability in dosing ranges (0.51-3.15) mg/kg in our results, this could be explained by the differences in providers' preference for the use of hydroxyzine as a sedative agent; especially, when used with more powerful agents such as meperidine and diazepam.[20] According to project USAP, the use of hydroxyzine also showed some discord in preferred dosing ranges, 37% preferred 2 mg/kg, whereas 36% preferred 1mg/kg, and close to 25% reported using a range of lower and higher doses.[34] The Cochrane review further proves the lack of consensus on the most effective dose for

Hydroxyzine.[14] A study by Shapira et al. has found that when hydroxyzine was added to midazolam sedation, it reduced crying and movement of pediatric patients,[35] however, the Cochrane review showed conflicting results in terms of effectiveness.[14] The published literature shows consensus with the results of our study as hydroxyzine shows the widest range in preferred dosages and lack of association with success or behavior.

Different medication dosages are presumed to have different effects on patients' behavior. In our study, the association between medication dosages of the triple diazepam, meperidine, and hydroxyzine was not significantly related to Frankl scores during the sedation. However, when data was adjusted for other patient variables (age, Frankl at Consult), a significant association was found between meperidine dose and sedation visit outcomes (behavior and success). This can indicate that, when used within the recommended dosing ranges, different medication dosages alone do not dictate patient behavior during sedation. Additional patient characteristics, especially age and Frankl at consult, are better predictors of sedation success and behavior. A study by Olacke et al. also showed no significant difference in terms of success related to the MMH sedation regimen dosages when reduced dosages to a scaled body weight of a sedation regimen were compared to dosages calculated at total body weight.[36] This can suggest that for both the MMH and DMH regimen, dosages of these medications alone are not predictors for the success of the sedation visit.

Different modalities of dental treatment have been suggested to influence the success and failure of pediatric dental sedations. In our study, the association of extractions with the triple regimen DMH was closely examined for any contributing effects. The results show no significant association between extractions and the odds of sedation success/failure. However, a statistically significant association between "Good Sedation Behavior" and extractions is

noticed. The “Good Sedation Behavior” accounted for 77% of all extraction cases (Frankl 3=43%, Frankl 4=34%). Important to note that increased “Good Sedation Behavior” with extraction cases can be due to many factors including a possible increased dosage of meperidine. The association between extraction visits and meperidine dose was not specifically analyzed in our study. Conversely, “Poor Sedation Behavior” noted less extraction cases which can be explained by the inability to complete planned extractions due to the patient's behavior and eventually deferring completion to another clinic visit or under general anesthesia. A study conducted in Brazil to measure the association of dental treatment type in regards of dental anxiety and behavior, showed no association between tooth extractions and patients’ anxiety and other factors such as patient behavior at consult visit and age were considered better predictors.[39] In another retrospective paper that studied the regimen (meperidine and hydroxyzine), a comparison between treatment location (anterior vs. posterior treatment) also appeared not to be associated with the results of the sedations.[26] Extractions did not demonstrate a significant association with success and behavior, but other treatment characteristics or nature can be evaluated and considered in future studies.

Behavior and temperament of patients have been suggested to be a predictor for acceptance of dental treatment and success of sedations.[37] Analysis of Frankl Behavior Rating Scale (FBRS) recorded at consult visit did not demonstrate statistical significance in terms of change in score at sedation visit (Table 3). Rather, successful treatment was associated with Frankl score at the consult appointment ($p = 0.0140$). An example that when patients received Frankl score 3, majority of these patients will remain a Frankl score 3 during sedation visits. This brings attention that if a patient presents with poor cooperation at evaluation visit, moderate sedation with DMH will not have great impact in improving behavior. These results can further

support established literature for moderate sedation that patient selection is the most important in predicting better sedation appointments.[26,37,38] Limited insurance coverage for general anesthesia, which is better suited for patients with poor cooperation, can be a major reason why providers choose to moderately sedate a patient with poor behavior at consult visits. At times, insurance companies will require a patient to fail a sedation visit, to become eligible for general anesthesia, regardless of presenting behavior. This highlights the ethical dilemma of providing patients with options that are unlikely to be successful when the indicated route for care is not feasible due to financial circumstances and insurance coverage.

Although a higher percentage of sedations were considered successful (89%) in terms of completion of definitive treatment, 29% of sedations recorded a Frankl 1 or 2, deeming them as "Poor Sedation Behavior." A continuing disagreement in terms of sedation success is noted in published studies, where some providers defined success as completion of dental treatment regardless of patient behavior during sedation visit, and others defined success when the patient displayed positive behavior during the sedation.[28] Figure 1 shows the patterns of behavior at consult appointments when compared to sedation visits. A statistically significant association was found such that, when patients scored a Frankl 1 or 2 at their sedation evaluation visits, they were 3.3 times more likely to have a "Poor Sedation Behavior" outcome. Patients with an initial Frankl 1 or 2 were also 2.2 times more likely to achieve an "Unsuccessful/Failed Sedation," where no definitive treatment was completed. This agrees with literature that suggests that parental rating of children's characteristics, especially emotionality and impulsivity, can predict their response under sedation.[26,38] Many other studies confirm that behavior at the consult visit is one of the most consistent predictors of better sedation appointments.[33,38] It is also important to mention that "Unsuccessful Sedations" received Frankl 1 scoring and they accounted for 10% of

the “Poor Sedation Behavior” cases. The results of our study further support available literature that patient selection is one of the most important predictors of sedation success even when using the DMH regimen.

Data analysis of first and second sedations showed that 17% of patients who underwent triple combination sedation had a second sedation visit, and only 2% of patients had subsequent (3 or more) sedation visits. This can be explained that when more extensive dental treatment is needed, general anesthesia would provide a safer and more cost-effective option by limiting the number of sedation visits required to complete treatment. A study found that when four or more sedations are expected, general anesthesia is a better route in terms of cost-effectiveness.[39] It is also important to note that once a patient experiences a failed sedation, he or she would be referred to general anesthesia for subsequent treatment. Inclusion of these subsequent sedation visits may increase the overall success rate as only those with a successful sedation would experience subsequent sedation visits. Overall, the number of subsequent sedation visits is influenced by the best standard for care along with patient tolerance.

A retrospective study has certain benefits in the field of pediatric dental sedation. These studies establish baseline associations where further areas of research, especially randomized control trials, can be executed to reach the best results and conclusions.[40] A retrospective study is especially valuable when studying pediatric patients who are considered a vulnerable population. Feasibility of strong randomized controlled trials can be challenging due the safety and ethical responsibilities that need to be accounted for when sedating the pediatric patient.

This is a retrospective study and is subject to all biases of a cohort chart review, since the data collected was not calibrated for the analysis of this study. Therefore, findings from this study cannot be generalized into a cause-effect relationship and careful assessment of results is

recommended. Due to the nature of this study, many biases and confounding factors might not be accounted for, such as recall bias when relying on provider notes documented in dental health records after the treatment, especially given the subjective nature of data like Frankl scores. The Frankl Behavior Rating Scale that was used to iterate results of "Good Sedation Behavior" compared to "Poor Sedation Behavior" is again a subjective scale, hence data cannot be objectively analyzed, however, it was used in this study due to its retrospective nature and the routine use of this scale in pediatric dentistry documentation of visits as it is easy to use by providers. An objective scale such as a Houpt Sedation Rating Scale can aid in eliminating some of the unintentional bias by providers in future studies.[41] This study reviewed the dental charts of a residency program where many providers and training residents conducted the sedations while under the supervision of multiple faculty members, each with different training and expertise in respect to moderate sedation. Moreover, analysis of second sedations could possibly reveal additional biases due to a "Successful" previous sedation, whereas failed sedations do not receive a subsequent sedation visit, to account for this bias, sensitivity analyses were performed on first sedation visit data (n=324) for both success and behavior.

Another limitation in regards to pharmacokinetics as sedation medications work synergistically and effects of medications can be difficult to assess individually when used in combination.[31] In this study the medications were assumed to be independent by statistical analysis methods, which may overestimate the effect of single medications. A clinical trial with controlled dosages of the triple medications can aid in assessing the effects of these medications when used in combination. Another factor to consider is the use of nitrous oxide analgesia during sedation which can also achieve synergistic effects when used with sedation medications. Future research can help evaluate the depth of sedation when using different nitrous oxide levels in

relation to successful sedations and improved sedation visit behavior. The use of passive immobilization during sedation is sometimes utilized at VCU Pediatric Dental Clinic. Indication for use are usually a rapidly declining patient behavior during sedation visit that might cause risk to patient and provider. The use of immobilization was not accounted for in the study. A research question that evaluates the effect of passive immobilization on sedation success and patient behavior during sedation can provide valuable data to pediatric dentists.

Further limitations can arise from the nature of the population where the chart review is conducted. VCU pediatric dental clinic is a training program that can be a final destination for pediatric patients who have not achieved good levels of cooperation in other dental offices. A traumatic or negative experience usually is associated with a previous failed dental visit. Moreover, a majority of patients seen in training programs are of lower socioeconomic status, therefore, data of this study might not be representative of all populations. Additionally, research shows that lower socioeconomic status can be associated with different parenting styles[42] that can have an effect on patient cooperation levels. Further studies can help in assessing if sedation success and sedation behavior improves or decreases with different populations in comparison to our study in order to measure the effect of population on the success of the DMH regimen.

A deficiency in good quality literature assessing pediatric dental sedation is evident.[34] Randomized control trials are encouraged to evaluate the effectiveness of other sedation regimens and medication dosages. As the medical and dental field continues to evolve in terms of preferred medication, these trends have to be evaluated carefully when it comes to the pediatric population.

Assessing effectiveness of the moderate sedation regimen (diazepam, meperidine and hydroxyzine) adds valuable knowledge to practitioners to help in patient selection, as well as, medication dosages. As providers attempt to dose medications subjectively, this study suggests that other factors are better predictors of sedation success and improved sedation behavior, such as age and positive patient behavior at evaluation visit. In conclusion, this research demonstrates that the triple regimen is an effective and valid regimen in achieving good and successful sedations for the majority of cases included. The findings of this study provide a basis for future studies to compare and establish effectiveness of this and other regimens.

Conclusion

1. This study shows that the diazepam, meperidine, and hydroxyzine (DMH) regimen is an effective moderate sedation regimen.

2. Patient age and Frankl Behavior Score at consult were significantly associated with both sedation success and sedation behavior. These results highlight the importance of patient selection for conscious sedation. Older patients and those with higher Frankl Behavior scores at previous dental visits were more likely to have positive outcomes (treatment success and behavior).

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