2019

Likability and Efficacy of Gummy Oral Sedative by Pediatric Patients

Marisol Carbonell
Nova Southeastern University

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Marisol Carbonell, D.M.D.

A Thesis Presented to the Faculty of the College of Dental Medicine of

Nova Southeastern University in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

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Approved as to style and content by:

APPROVED BY: _____

Judith Chin, D.D.S., M.S. (Committee Chair) Date

APPROVED BY: _____

David Mastropietro, Ph.D., R.Ph. (Committee Member) Date

APPROVED BY: _____

Margaret Kim D.D.S., M.S. (Committee Member) Date

APPROVED BY: _____

Linda C. Niessen, D.M.D., M.P.H. (Dean, College of Dental Medicine) Date

NOVA SOUTHEASTERN UNIVERSITY | NSU Florida
Health Professions Division
Department of Pediatric Dentistry
College of Dental Medicine

STUDENT NAME: Marisol Carbonell, D.M.D.

STUDENT E-MAIL ADDRESS: Maricarb@mynsu.nova.edu

STUDENT TELEPHONE NUMBER: (305) 890-6706

COURSE DESCRIPTION: Master of Science

TITLE OF SUBMISSION: Likability and Efficacy of Gummy Oral Sedative by Pediatric Patients.

DATE SUBMITTED: June 30, 2019

I certify that I am the sole author of this thesis, and that any assistance I received in its preparation has been fully acknowledged and disclosed in the thesis. I have cited any sources from which I used ideas, data, or words, and labeled as quotations any directly quoted phrases or passages, as well as providing proper documentation and citations. This thesis was prepared by me, specifically for the M.Sc.D. degree and for this assignment.

STUDENT SIGNATURE: _____

Marisol Carbonell, D.M.D. Date

DEDICATION

To my husband, Jason, and crazy kids, Jayden and Leah, thank you for all of your love and support throughout this journey.

ACKNOWLEDGEMENTS

I would like to thank my mentor, Dr. Judith Chin, for her continued support of this project. Her knowledge and persistence has allowed us to conduct meaningful research that will impact the way we care for our patients.

Next, I would like to thank Dr. David Mastropietro for his expertise with the pharmacological aspects of the project, as well as his guidance with the writing process. Without his willingness to help and prompt action, this project would not have been possible.

I also thank my faculty and co-residents who helped me complete this project by actively participating in the data collection process in clinic. Your shared enthusiasm was greatly appreciated.

Finally, I would like to acknowledge NSU HPD, whose support through grant funds allowed us the opportunity to conduct this research.

ABSTRACT

LIKABILITY AND EFFICACY OF GUMMY ORAL SEDATIVE BY PEDIATRIC PATIENTS

DEGREE DATE: JUNE 30, 2019 Marisol Carbonell, D.M.D.

COLLEGE OF DENTAL MEDICINE NOVA SOUTHEASTERN UNIVERSITY
Judith Chin DDS, MS, Director, Pediatric Dental Residency Program, NSU College of Dental Medicine

Background: Behavior guidance of the pediatric patient remains a challenge in dentistry and may require pharmaceutical interventions. Midazolam and hydroxyzine oral syrups are predictable and frequently used for in-office sedations in pediatric dentistry. However, midazolam's bitter taste and hydroxyzine's large volume make administration problematic for uncooperative children. The purpose of this project was to compare the use of soft-chewable gummies containing sedatives to the oral syrups currently used in conscious sedation. The aim of this project was to administer midazolam and hydroxyzine in gummy form and determine if this alternative vessel is as effective and better liked by children undergoing sedation when compared to the respective oral syrups.

Methods: Small-sized gummies containing 2.5 mg of midazolam or 5.0 mg of hydroxyzine were optimized for taste masking and compounded at the NSU pharmacy. A pilot study was conducted at NSU's Joe DiMaggio Dental Clinic to test the likability and the effectiveness of these gummies. A convenience sample of 20 patients requiring conscious sedation were evaluated and determined eligible to receive sedation by gummies for the test group. A cohort of 20 patients

previously administered syrup sedatives served as the historical control. In both groups, the sedative agent and dose were selected and calculated based on patient specific parameters and anticipated duration of treatment. Sedation onset time was recorded for each patient along with a score obtained from a hedonic scale evaluating patients' likability of the different medications.

Results: For the midazolam group, data obtained from the historic cohort, was compared to the data obtained from the participants of the clinical trial. A small sample size did not allow for categorizing patients based on demographics, however there were no significant differences between both groups. The midazolam gummy group had a greater frequency of higher hedonic scale scores, however, the finding was not statistically significant. The onset time for the midazolam gummy group was also slightly shorter, but also not statistically significant. Results for the midazolam and hydroxyzine group are not available due to insufficient data and low number of participants.

Conclusions: Oral sedation is an alternative method of behavior guidance used by pediatric dentists. The targeted population often rejects the medication, compromising the sedation. More favorable methods of administering medications are necessary. Research using compounded medications and clinical trials with the pediatric population must continue to optimize the final product.

Key words: Oral Conscious sedation, Midazolam, Hydroxyzine, Pediatrics, Gummy, Compounding

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ABBREVIATIONS

ANOVA	Analysis of Variance
ASA	American Society of Anesthesiologists
CNS	Central Nervous System
HCl	Hydrochloride
IV	Intravenous
L	Liter
mg	Milligrams
mL	Milliliters
mm	Millimeters
NPO	Nothing by Mouth
NSU	Nova Southeastern University
pH	Potential of Hydrogen
USP	United States Pharmacopeia

CHAPTER 1 INTRODUCTION

1.1 Background

Behavior guidance of pediatric patients remains a challenge in dentistry. A survey administered to US board certified pediatric dentists corroborated the belief that changes in parenting styles have affected treatment modalities, resulting in much less use of assertive behavior guidance techniques.[1] Consequently, pharmaceutical techniques are frequently used to supplement behavior guidance. Deep sedation or general anesthesia may be indicated for cases requiring extensive treatment, while conscious sedations may be more appropriate for in-office management of less extensive cases.

Although the oral medication route is predictable and practical for dental cases, administration of oral sedative syrups is problematic for uncooperative children. This problem is compounded by the fact that these medications can have a very unpleasant taste (e.g., midazolam) or require a large volume to be swallowed in meeting the dosing requirements (e.g., hydroxyzine). Therefore, a need exists to develop and evaluate means for administration of sedative medications that can overcome the problems with administration of the current liquid formulations.

1.2 Drug Selection/ Midazolam

Midazolam is currently the benzodiazepine of choice for in-office sedations in pediatric dentistry. It was first introduced in 1976 by Fryer and Walser. [2] It is a

selective CNS depressor which acts by opening GABA mediated chloride channels. When compared to diazepam, which has active metabolites and a long half-life, midazolam has a much shorter half-life and its metabolites have little to no pharmacologic activity. After oral administration in children, midazolam is rapidly absorbed and undergoes extensive metabolism in the liver, with an elimination half-life of approximately 40-60 minutes. In dentistry, it is used particularly for the therapeutic benefits of anterograde amnesia, anxiolysis, sedation and hypnosis. Although it may cause respiratory depression, there is a wide safety margin between a therapeutic dose and a toxic dose. [3] Midazolam is a short-acting sedative agent with a high safety margin and a readily available reversal agent, properties that make it suitable for the use of in-office conscious sedations in pediatric dentistry. [2]

1.3 Route of Delivery/ Midazolam

Midazolam is approved in United States for administration by the oral and parenteral routes. Other off-label routes include intranasal, sublingual/buccal, and rectal.

Intravenous: The administration of midazolam by parenteral routes bypasses the extensive first pass metabolism effects of the liver and produces a rapid onset of action (1.5 to 5 minutes) and a working time of 20-60 minutes. While the efficacy of the IV route is known by many pediatric dentists, it is often not feasible with children that suffer from dental anxiety and fear.

Intranasal: The administration of intranasal midazolam also bypasses the extensive first pass metabolism effects of the liver. It has an onset time of 10-15 minutes and a working time of approximately 10-25 minutes. This method of delivery is associated with ease of administration and compliance, requiring little time for administration. However, studies show that 61-74% of patients will cry during administration of intranasal midazolam.[4] This discomfort felt by the child may have an opposite effect and increase the patient's anxiety.

Sublingual/Buccal: Midazolam is absorbed through the oral mucosal with onset of action for the buccal cavity being approximately 20-30 minutes. These routes of delivery have not found traction in the field of pediatric dentistry. The reasons may be due to the fact that younger children often have trouble following directions, especially when normal reflexes have to be overcome.[4,5]

Rectal: There is a discrepancy amongst studies in regards to the recommended dose, ranging from 1 mg/kg to 0.25-0.35 mg/kg.[2] [6] Regardless, the child or parent may find it uncomfortable or distressing to use this route, especially in a dental setting. [6,7] For these reasons, rectal administration has not been embraced in the US by pediatric dentists.

Oral: After oral administration, midazolam undergoes first pass metabolism, reducing the bioavailability. Therefore, only 15% to 30% of a dose will reach the systemic circulation. For this reason, the oral dose administered is higher

compared to other routes. Oral doses range from 0.3- 1.0 mg/kg and typically have a slow onset of anxiolytic and sedative effects, occurring within 20-30 minutes.[5] This route has other limitations for pediatric patients, for example, a child may spit out all or most of the medication due to its unpleasant taste. Even if the child swallowed most of it, the provider will likely not reach proper sedation and will be unable to give a second dose due to the uncertainty of the ingested amount. According to the American Academy of Pediatric Dentistry, the oral route is the most accepted route by children.[8] Therefore, for this study oral administration was chosen as the preferred route.

1.4 Drug Select Hydroxyzine

Hydroxyzine is another common agent used in sedations because of its minimal other drugs such as midazolam for longer in-office procedures.[9] Hydroxyzine is a first-generation antihistamine (H1 receptor antagonist) with sedative properties.[10] It is commonly prescribed to children for allergic diseases with drowsiness and decreased alertness (mild sedation) reported as a common side effect.[9] Hydroxyzine also has antiemetic, antispasmodic and anticholinergic effects. Although it has a wide safety margin, when used with other central nervous system depressants it can enhance the depressant effect.[11] Doses studied for the use of sedation in the pediatric population range from 1-2 mg/kg.[11] When using the commercially available 10 mg/5 mL oral syrup, this can result in a large volume of liquid for a pediatric patient to ingest.

1.5 Current Limitations

There are three major limitations to using oral sedatives such as midazolam and hydroxyzine in the pediatric population:

1. *Aversion to Administration*: Medications presented in a medicine cup or oral syringe are often associated with anxiety and apprehension, especially in uncooperative children. Several studies have reported a positive correlation between the patient's willingness to take the medication, and the outcome of the sedation.[11,12] Therefore, increasing the acceptance of the medication may contribute to the success of the sedation.

2. *Aversion to Taste*: Midazolam has bitter taste that is very difficult to mask. Previously, it has been mixed with fruit juices, soda, or other flavored drinks in an attempt to improve acceptance.[13] However, children continue to have difficulty swallowing the entire dose and a high level of rejection persists with these prepared formulations.

3. *Limited Dosage Forms in Pediatrics*: The aversive taste of a medication can be overcome by dispensing it in a tablet or capsule. However, children often have difficulty with tablets and capsules because they cannot swallow them properly and lack experience.[14] Despite knowing this, there continues to be few pediatric formulations to address administration

problems.[15]

1.6 Literature Review of Formulation Designs

The unpleasant taste of medications is one of the most common causes of non-compliance among pediatric patients for orally administered drugs.[16] As such, additional delivery methods have been studied to mask the taste of bitter medications using pediatric-friendly dosage forms.

Intranasal: Intranasal formulations of midazolam have been used in an attempt to avoid the bitter taste and increase acceptance rates. For example, Manoj et al. compared the acceptance of oral versus intranasal midazolam.[17] This study reported that the oral liquid was more accepted by children, likely due to a burning sensation from the nasal route.[17]

Oral: Recently, a hospital in Australia reported success in masking the bitter taste of midazolam by compounding it with a chocolate base into chewable chocolate tablets. [18] Similarly, Lenahan et al. reported higher acceptance rates for hydroxyzine pills crushed and mixed with a flavoring agent. [11] However, the study showed that approximately 11% of the time patients were still non-compliant. They also reported success rates dropping significantly when a portion of the medication was expectorated. Rosen and Rosen reported that the preferred vehicle in their pediatric intensive care unit, operating room, and clinics at the University of Michigan Medical Center was midazolam injection mixed with

flavored gelatin (with sugar) that was solidified in ice-cube trays. This method was most favored by children compared to mixing the injection solution in partially melted commercially available popsicles, orange juice, apple juice, cherry and banana flavor extracts, chocolate syrup, crème de marshmallow, and cola.[19]

1.7 Research Opportunity

Most of the research available for hydroxyzine or midazolam in the pediatric population evaluates the efficacy of the drug as a sedative agent or evaluates different routes of administration. In 2018, a study conducted by Cheung et al. evaluated the palatability of midazolam compounded into chocolate tablets. In this study, chocolate was used because of its ability to mask bitterness and improve the presentations of the sedative. Rosen and Rosen reported that the preferred vehicle in their pediatric intensive care unit, operating room, and clinics at the University of Michigan Medical Center was midazolam injection mixed with flavored gelatin (with sugar) that was solidified in ice-cube trays.[19] However, to our knowledge no previous research has evaluated midazolam or hydroxyzine compounded into gummies.

There was also no research found in regard to NPO status when using gummy medications. On this subject, Dr. Sandra Kaufman, a board-certified anesthesiologist and Chief of Services for Pediatric OR at Joe DiMaggio Children's Hospital, was consulted. She stated she had no safety concern

involving the use of gummies prior to sedation. Dr. Jeff Browstein, a board-certified pediatric dentist and dental anesthesiologist, was also consulted and communicated that he also had no safety concerns over breaking NPO status with the sedation gummies.

1.8 Research Goals and Objectives

For both sedatives, the main obstacle is the patient's willingness and cooperation to take the medication. In this study, the objective is to overcome these obstacles with the help of compounding pharmacology by using gummies as a vessel. The goal of this project is to develop effective midazolam and hydroxyzine gummies that are palatable and therefore, easier to administer than the suspensions.

1.9 Specific Aims

In this study, we had 2 specific aims:

1. To determine children's likability of midazolam and hydroxyzine gummies used for sedation.
2. To evaluate sedation (efficacy) parameters after administration of hydroxyzine and midazolam gummies by oral route.

1.10 Hypotheses

In this study, we tested the following hypotheses:

1. Whether medicated gummies are appealing, accepted, and liked by children.

2. Whether midazolam and hydroxyzine gummies provide onset times equal to those in liquid form for children.

Null Hypotheses:

1. Medicated gummies are just as appealing, accepted, and liked by children as the respective syrup forms of the medications.
2. Midazolam and hydroxyzine gummies provide onset times similar to those in respective syrup form for children.

Alternative Hypotheses:

1. Medicated gummies are more appealing, accepted, and liked by children than the respective syrup forms of the medications.
2. Midazolam and hydroxyzine gummies provide onset times different to those in respective syrup form for children.

CHAPTER 2 MATERIALS AND METHODS

2.1 Materials

Hydroxyzine HCl and midazolam HCl gummies were compounded at the NSU pharmacy using commercially available sources of the drugs or pharmaceutical grade bulk powders (Figure 1). The drug doses were standardized in each gummy (2.5 mg for midazolam and 5.0 mg for hydroxyzine) to meet the sedation needs of patients based on weight using one or more gummies. The chewable gummy base consisted of gelatin, simple syrup, flavoring, and sweetener. Bitter masking of the drug in the formula was optimized using bitter suppressing agents, organic acids, sodium salt and/or other known ingredients commonly known in the art of compounding. The flavor used for the gummies was "Tutti Frutti".

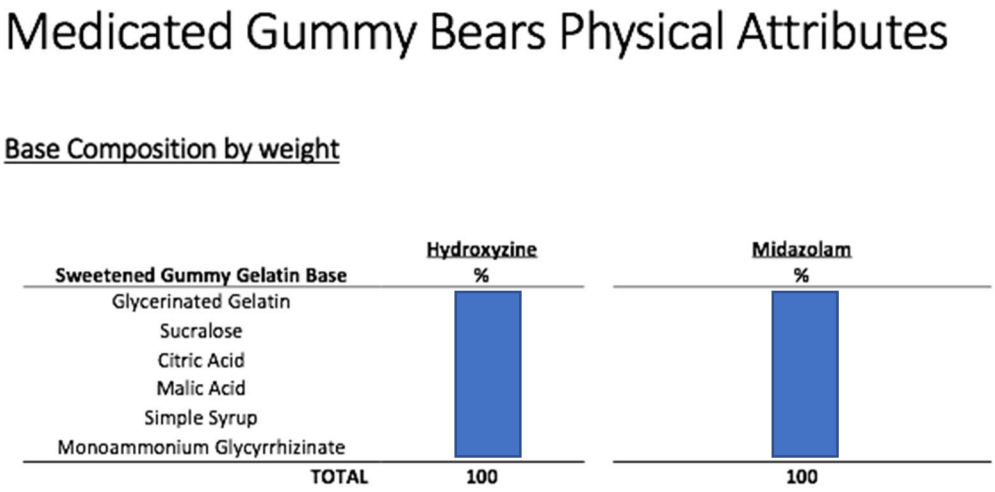


Figure 1. Physical attributes of medicated gummy bears

2.2 Method of Preparation

During preparation, the formula was melted and poured into molds resembling bears. This process, known as fusion, allows the drug and other components to dissolve or disperse in the melted base. The final product was a gummy bear approximately 18 mm in length, 10mm in width, and 10mm in thickness (Figure 2). The color varied slightly for each medication.

Packaging: The gummies were individually wrapped in foiled paper and packaged in a tight, light-resistant container.

Labeling: The label stated “use only as directed, store in refrigerator, must be chewed before swallowing”.

Storage: The medication was stored in a locked refrigerator for medications only.

Refer to Appendix C for compounding procedures and Appendix D for a sample of the compounding record used for documentation.

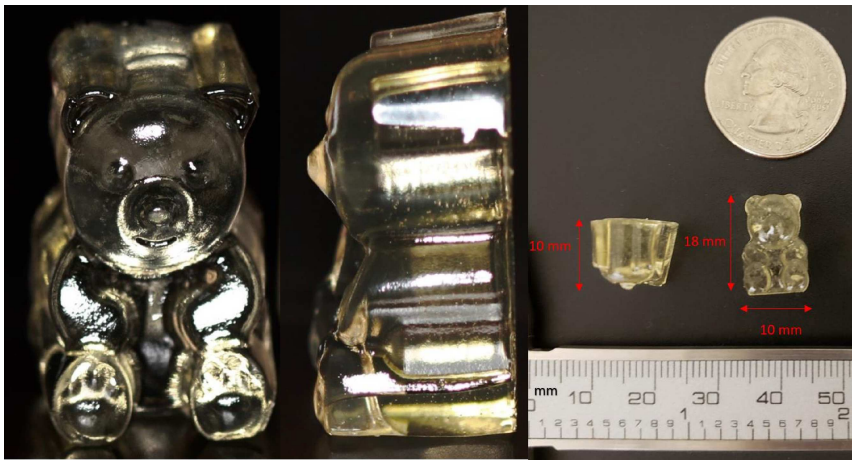


Figure 2. Gummy bear example

2.3 Overall Study Design

The participation population of the study resulted from the convenience and natural inflow of patients from NSU's Pediatric Dental clinic at Joe DiMaggio Children's Hospital that needed sedation and from a historic cohort of previous sedations done in the same clinic. The sedation check list was used to determine if patients were sedation candidates (Appendix E). Parents were informed of the medication vehicle during the sedation consultation and during the sedation appointment. If they agreed to participate in this study, informed consent was obtained. For patients 8 years old and older, assent was obtained.

Base line vitals (blood pressure and oxygen saturation) were obtained before initiating the sedation. The participants were given the gummies containing the sedative medication and instructed to chew the gummy before swallowing. The sedation monitor observed the child chewing the gummy and recorded whether the patient took the medication, partially took it, or did not take it at all. Only the patients who took the medication were included in the study. After ingestion, the patients were asked to rate the gummies using a five-point hedonic scale (Figure 3). Vitals were recorded at a 5-minute interval. The data collected for the midazolam gummy group and the midazolam plus hydroxyzine gummy group was compared to previous data collected using the respective syrup formulas.

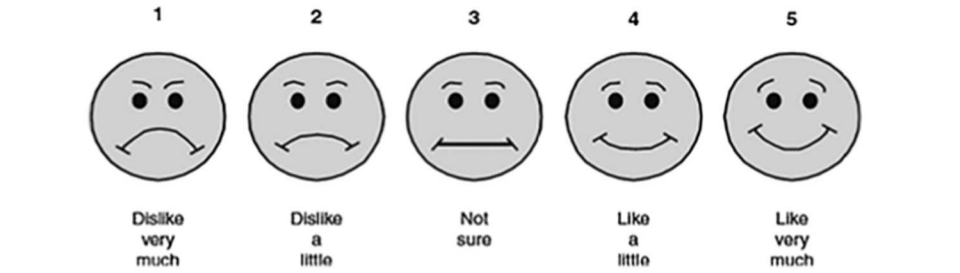


Figure 3. Hedonic scale

2.4 Monitoring of Sedation

If the patient refused to take the medicated gummies, the sedation continued with the syrup form. Patients that partially ingested the gummies (e.g., spit a portion out) were continuously monitored until all the discharge criteria was met (Appendix F).

All patients in the study were monitored during the sedation in accordance to the standard of care established by the American Academy of Pediatric Dentists. The onset of sedation and continued levels of sedation were recorded on the sedation record sheet by the attending pediatric dental faculty or resident every five minutes, and were categorized as none, minimal, moderate, deep, or general anesthesia. The level of sedation was determined by the patient's responsiveness in accordance to the Continuum of Depth of Sedation provided by the American Society of Anesthesiologists.[20]

2.5 Selection of Sedative Agent

Selection of the sedative agent was based on the anticipated duration of treatment, with midazolam usually used for short procedures (extractions, one to

two surface restorations, stainless steel crowns), and a combination of midazolam plus hydroxyzine used for longer procedures (pulpotomies and stainless-steel crowns, multiple quadrant dentistry).

The sedation dosage for midazolam in the study ranged from 0.23 to 0.5 mg/kg. The sedation dosage for hydroxyzine ranged from 0.3 to 0.68 mg/kg. The appropriate dosage for each individual was selected and the number of gummies necessary was calculated.

Example:

A 0.5 mg/kg dose of midazolam for a child weighing 20 kg would be calculated as follows:

20 kg x 0.5 mg/kg = 10 mg of midazolam

The corresponding number of individual gummies would be calculated as follows:

1 gummy = 2.5 mg midazolam/gummy

10 mg x (1 gummy/2.5 mg midazolam) = 4 gummies

2.6 Sample Size

Anticipated sample size: 40 patients

20 Sedation records where the liquid medication was used in the past (historic cohort)

- 10 records of patients who used midazolam suspension
- 10 records of patients who used midazolam and hydroxyzine suspension

20 New patients undergoing sedation using gummies

- 10 patients using the midazolam only gummy
- 10 patients using the midazolam and hydroxyzine gummies

2.7 Variables

Dependent Variables:

Acceptance of the midazolam and hydroxyzine liquid and gummies using the five-point hedonic scale.

The effectiveness of the sedation with liquid and gummies using onset time.

Independent Variables:

The patient's demographics (gender, age), dental history (number of sedations for dental treatment), and the dosage of medication administered.

2.8 Criteria

Inclusion:

Patients who meet the criteria for oral sedation at NSU's Joe DiMaggio Dental Clinic using midazolam only or midazolam and hydroxyzine. These criteria include:

- Age: 3 years and older
- Airway assessment score of no more than Brodsky 2, and Mallampati II
- No limited neck mobility
- No micro/retrognathia
- No macroglossia

- No obesity (patients with a BMI of 85% or less)
- Patients who are ASA Class I or II
- Indication for sedation such as fear, situational anxiety, uncooperative behavior due to lack of maturity, physical or mental disability
- English speaking
- Charts reviewed for oral sedations using the syrup form of midazolam only, or midazolam and hydroxyzine
- Charts reviewed for patients who are ASA Class I or II

Exclusion:

- Patient's diagnosed with Autism Spectrum Disorder due to a similar study being conducted with this specific population
- Allergy or known hypersensitivity to any active or inactive ingredient in the gelatin gummies
- Charts reviewed that do not have a record of the hedonic scale
- Charts reviewed where the hedonic scale was not adequately completed

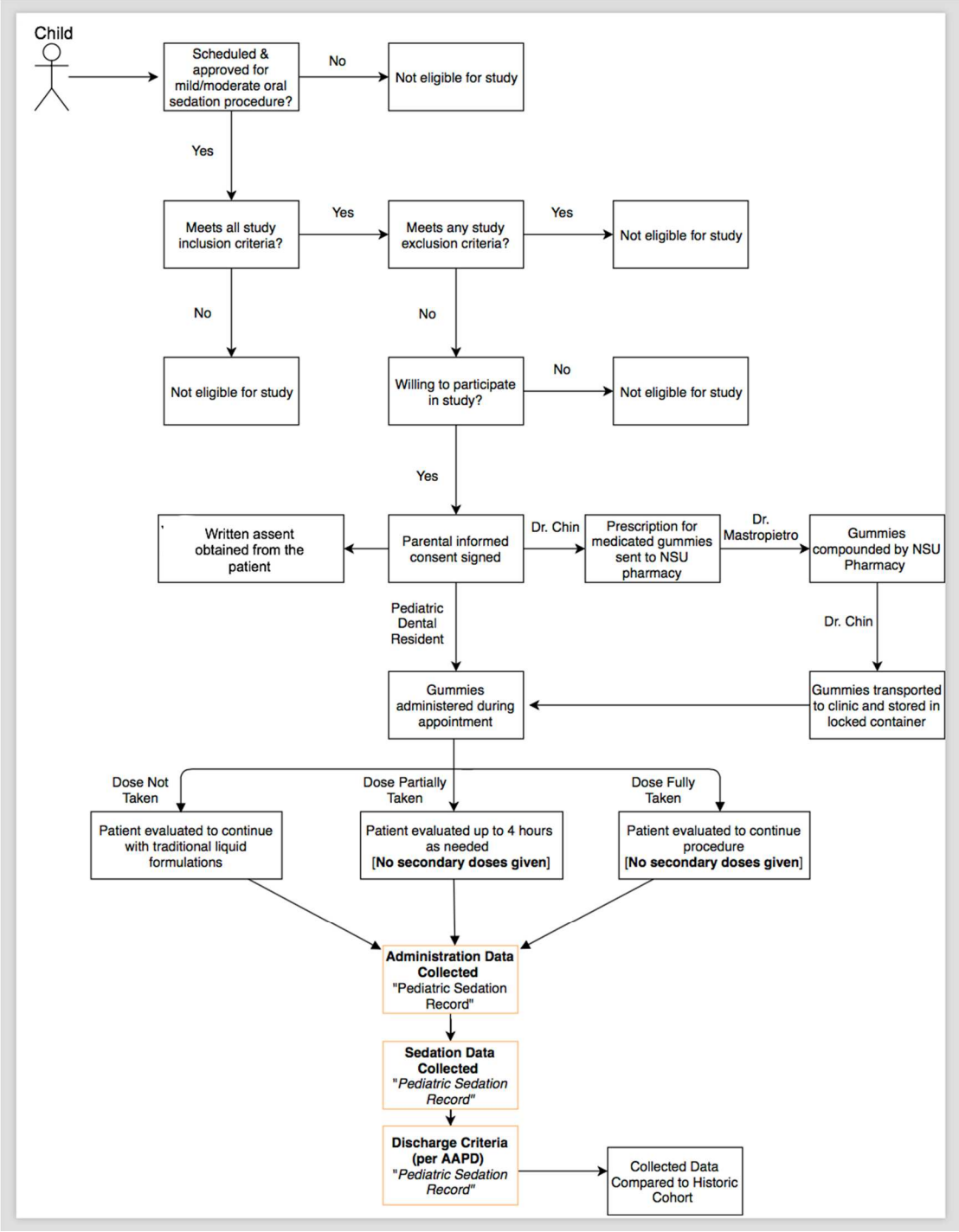


Figure 4. Sedation protocol flowchart

2.9 Statistical Analysis

Descriptive statistics were calculated for all study variables. Because these metrics were not normally distributed, or possessed heterogeneity of variance, nonparametric tests were conducted. To compare the acceptance of the midazolam and hydroxyzine gummies and the effectiveness of the sedation with syrup and gummies using onset time, a Van der Waerden test was conducted. The advantage of the Van Der Waerden test is that it provides the high efficiency of the standard ANOVA analysis when the normality assumptions are in fact satisfied, but it also provides the robustness of the Kruskal-Wallis test when the normality assumptions are not satisfied. JMP 14 SW used for all statistical analysis. Statistical significance was accepted at $p < 0.05$.

CHAPTER 3 RESULTS

3.1 Comparison of Midazolam Gummy and Midazolam Syrup

For this portion of the clinical study, data was collected from 10 records of patients who had the midazolam syrup (historic cohort) and 10 patients who had the midazolam gummy. Patient demographics are listed in Table 1.

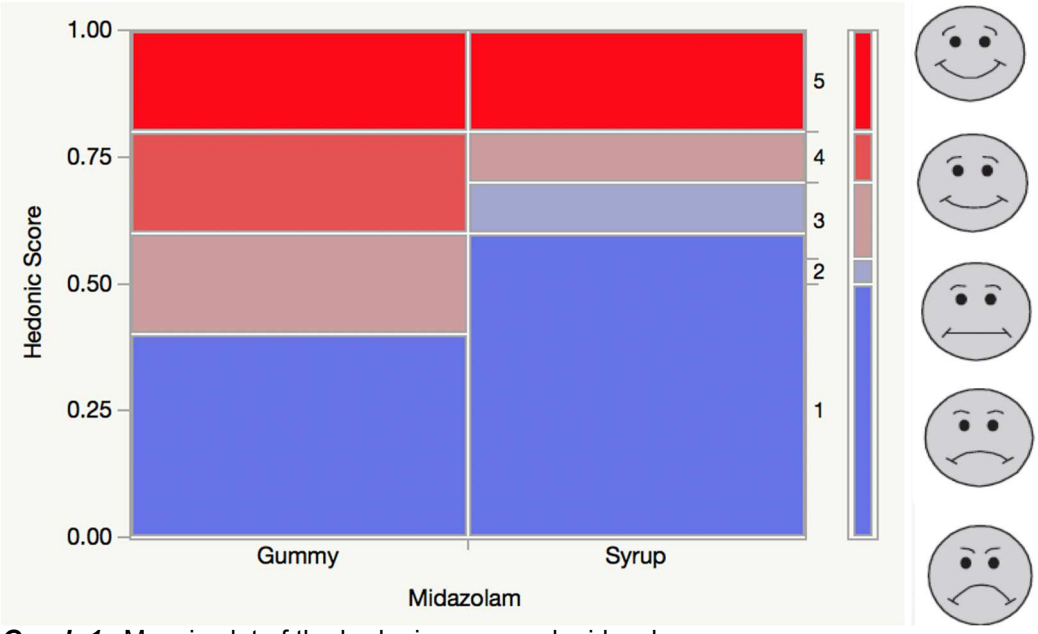
Table 1. *Analysis of the independent variables collected from 20 participants in the midazolam portion of the clinical study*

		Midazolam Gummy (n=10)	Midazolam Syrup (n=10)	*P* value (<0.05)
Age	Mean	6.00	5.70	0.6639
	SD	1.76	1.05	
Gender	Male	6 (60%)	6 (60%)	1.0000
	Female	4 (40%)	4 (40%)	
Dosage mg/kg	Mean	0.363	0.385	0.8215
	SD.	0.073	0.100	
# of Sedations		1 (80%) 2 (10%) 3 (10%)	1(100%)	0.3292

Due to the small sample size, the data was not categorized based on demographics. However, there were no significant differences in any of the demographic characteristics of the midazolam syrup group, versus the midazolam gummy group. Table 2 summarizes the data collected for the hedonic scale and onset time. A mosaic plot is provided as a visual illustration of the results for the hedonic scores (Graph 1).

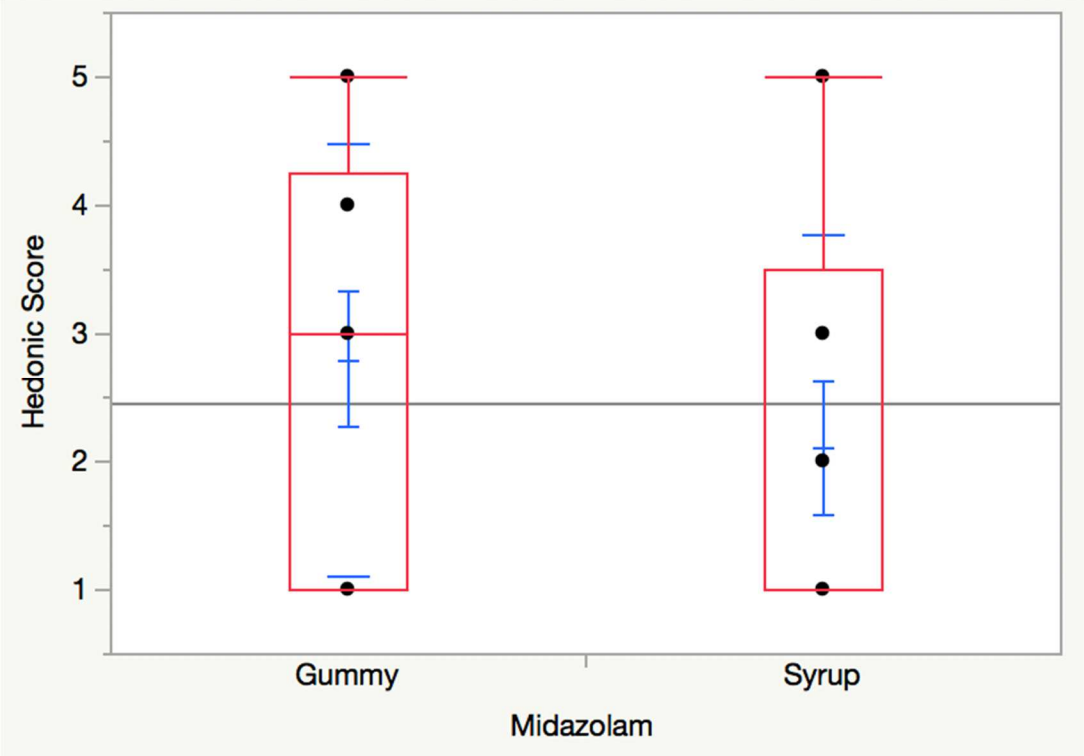
Table 2. *Analysis of the dependent variables collected from 20 participants in the midazolam portion of the clinical study*

		Midazolam Gummy (n=10)	Midazolam Syrup (n=10)	*P* value (<0.05)
Onset Time Minutes	Mean	16.60	18.10	0.6639
	SD	5.78	7.05	
Hedonic Score (1-5)	Mean	2.80	2.10	0.411
	SD	1.69	1.66	

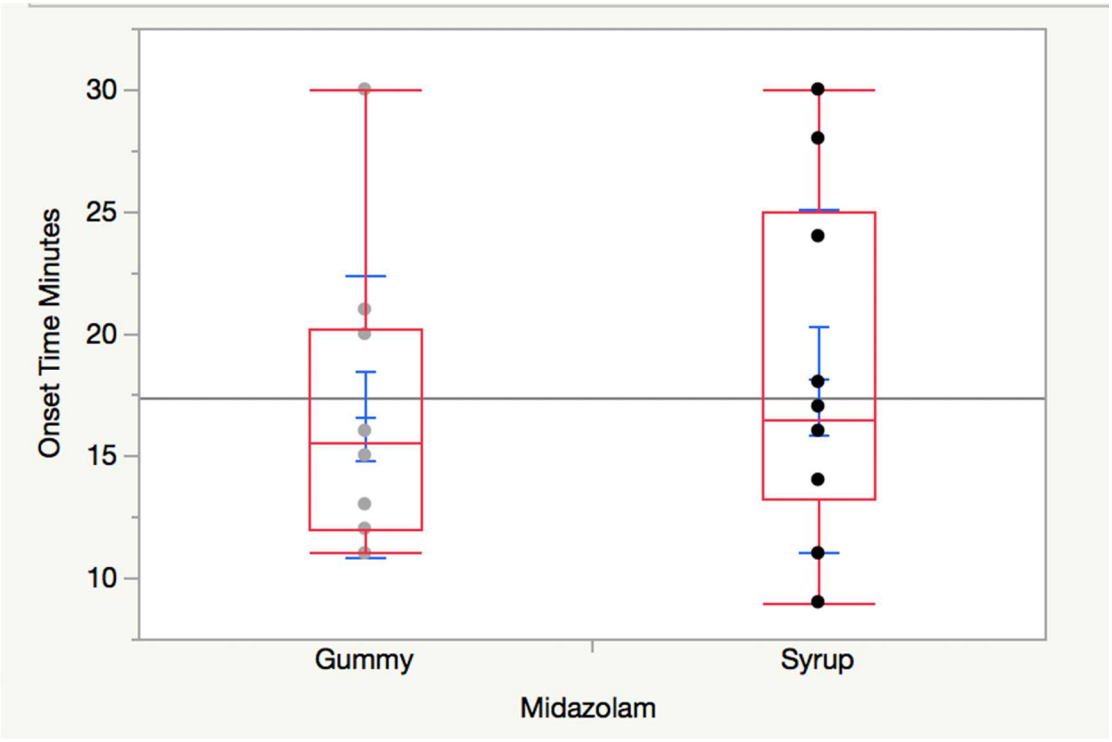


Graph 1. Mosaic plot of the hedonic score and midazolam groups

Nonparametric Van der Waerden tests were conducted to compare the acceptance and onset times for the midazolam groups. There was a preference for the midazolam gummies, though it was not statistically significant (Graph 2). The same test was conducted to compare the onset times. Although the gummy group had a faster onset time, it was also not statistically significant.



Graph 2. One-way analysis of variance box plots illustrating observed hedonic scores for selected vehicles containing midazolam



Graph 3. One-way analysis of variance box plots illustrating observed onset times by midazolam in selected vehicles.

3.2 Comparison of Midazolam Plus Hydroxyzine Gummy and Midazolam Plus Hydroxyzine Syrup

This portion of the study was intended compare the syrup and gummies used for midazolam and hydroxyzine. However, there were an insufficient number of patients (n=3) who received this treatment combination during the study timepoints to obtain a complete data set. Table 3 summarizes the findings for the 3 patients that received this sedation.

Table 3. *Data collected from 3 participants in the clinical study for the midazolam plus hydroxyzine groups*

	Midazolam and Hydroxyzine Gummy (n=1)	Midazolam and Hydroxyzine Syrup (n=2)
Gender	Male 0 (0%) Female 1 (100%)	Male 1 (50%) Female 1(50%)
Dosage mg/kg	Mean Midazolam 0.30 Mean Hydroxyzine 0.30	Mean Midazolam 0.42 Mean Hydroxyzine. 0.59
# of Sedations	1 (100%)	1 (100%)

CHAPTER 4 DISCUSSION AND CONCLUSIONS

4.1 Discussion

The clinical study did not yield any statistically significant results, likely because of the low number of participants. Recruiting participants for the midazolam plus hydroxyzine group was difficult because of the low frequency in which both medications are used together. As previously stated, midazolam and hydroxyzine are used in conjunction for longer procedures. However, patients requiring extensive treatment or complex procedures are more likely to be seen in the operating room under general anesthesia.

Recruiting participants was also challenging due to issues such as appointment cancellations or rescheduling due to health reasons (e.g., a recent upper respiratory infection). Moreover, writing prescriptions for each patient, the time necessary for making the gummy bears, transporting the gummy bears, and their short beyond-use dating (2 weeks) added to the complexity and expense of the study.

Although the data was not statistically significant, there was a trend of patients liking the midazolam gummy bears more than the syrup. Anecdotally, the participants also showed more enthusiasm and compliance prior to ingesting the gummy bears in comparison with the syrup. Additionally, we noticed an added benefit to the gummies which was clinically relevant and not anticipated at the beginning: If the patient spit out the medicated gummy bear, it was easier to

salvage, re-administer and continue with the sedation. With the syrup, if the patient spit out a portion of the medication, the dose was usually lost on the patient napkin or clothes. Since we are unable administer an additional dose, this could compromise the success of the syrup sedation.

Another positive outcome was the efficacy of the medication. The sedation onset times were very similar in comparison to the syrup. In fact, the gummy bears had a slightly shorter onset time (statistically insignificant). This may be due to increased solubility of the drug occurring from changes in local pH due to the acids in the gummy formulation; since midazolam is more soluble at lower pH values (e.g., <4). Another hypothesis is that the increased residence time in the mouth during chewing may lead to a portion of the drug being absorption through the oral mucosa.

Future clinical trials should streamline the process of ordering, making, and transporting the gummies. A longer timeframe is also necessary to recruit participants for the midazolam and hydroxyzine groups. Also, higher number of participants will help determine if the trends noted have statistical significance.

4.2 Conclusions

Oral sedation is an alternative method of behavior guidance frequently used by pediatric dentists. The population requiring sedation is often very anxious or uncooperative. Syrup medications are often rejected or spit out, compromising

the success of the sedation. Therefore, it is necessary to formulate an alternative sedation medication delivery system that is effective and better liked by children undergoing sedation in comparison to the respective oral syrup. Compounding medications to circumvent a bitter taste or large volume is a viable alternative that must continue to be researched. Clinical trials with the pediatric population are necessary to make necessary adjustments to the final product.

CHAPTER 5 RAW DATA

Midazolam Syrup

AGE / SEX	# OF SEDATIONS	mg/kg	HEDONIC SCORE	ONSET TIME	SEDATION LEVEL (N,M,MOD,D,G)
6/m	1	0.35	3	14	M
4/m	1	0.3	1	14	M
6/m	1	0.3	5	24	M
6/f	1	0.5	2	28	M
7/m	1	0.3	1	11	M
6/f	1	0.5	1	16	M
7/m	1	0.5	5	30	M
5/m	1	0.5	1	17	M
4/f	1	0.3	1	18	M
6/f	1	0.3	1	9	M

Midazolam Gummies

AGE / SEX	# OF SEDATIONS	mg/kg	HEDONIC SCORE	ONSET TIME	SEDATION LEVEL (N,M,MOD,D,G)
7/f	1	0.33	3	13	M
7/m	2	0.4	5	20	M
4/m	1	0.4	1	16	M
4/m	1	0.34	4	16	M
6/m	1	0.33	5	15	M
9/f	3	0.5	3	30	M
8/m	1	0.3	1	12	M
5/m	1	0.4	4	21	M
4/f	1	0.23	1	12	M
6/f	1	0.4	1	11	M

Midazolam Plus Hydroxyzine Syrup

AGE / SEX	# OF SEDATIONS	mg/kg	HEDONIC SCORE	ONSET TIME	SEDATION LEVEL (N,M,MOD,D,G)
10/m	1	0.34/0.68	3(M) 3(H)	18	M
9/f	1	0.5/0.5	3(M) 3(H)	12	M

Midazolam Plus Hydroxyzine Gummies

AGE / SEX	# OF SEDATIONS	mg/kg	HEDONIC SCORE	ONSET TIME	(N,M,MOD,D,G)
11/f	1	0.3 /0.3	2(M) 3(H)	15	M

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APPENDICES

Appendix A

Pharmacology Information Regarding Medicated Gummies written by Dr. David Mastropietro

Classification

Chewable gummies fall under the lozenge category of dosage forms. Lozenges are a type of solid or semi-sold dosage form that can be dissolved, disintegrated, or chewed in the mouth. Varies types of lozenges have traditionally been used as an alternative for the delivery of mediations to the oral mucosa (locally) and systemically after being ingested. They are advantage for patients since they are pleasantly flavored, sweetened, easily administered to those who have difficulty swallowing, and can facilitate administration to geriatric and pediatric patients.[21] They may also be considered more accurate for patient dosing when compared to measuring liquid formulations. There are three types of lozenges: Hard, Soft, and Chewable (gummy). It has been reported that gelatin gummy sweets and other soft chewable dosage forms may be easier, more appealing and natural to chew for children, compared to a chewable tablets.[22]

More recently, the term “Chewable Gels” has become the official nomenclature according to the United States Pharmacopeia (USP) for soft chewable gummy formulations designed to deliver drug substances or dietary supplements orally. Bioactive components have also been studies for delivery in gelatin chewable bases to help with taste and stability issues.[23] There are now 2 official USP

monographs developed for chewable gels and two more under development based on USP recognizing the need and growing market for these formulations.[24]

USP Monographs for Chewable Gels

- Ascorbic Acid Chewable Gels
- Cholecalciferol Chewable Gels
- Under Development
    - Cyanocobalamin Chewable Gels (submitted May-JUN 2018)
    - Oil-and Water-soluble Vitamins with Minerals Chewable Gels

There are limited manufactured prescription products in gummy formulations (e.g., Vitafol Gummies). Although patents on soft chewable gummies containing pharmaceutical ingredients are abundant.

Lozenges are also frequently compounded by pharmacies to meet specific needs of patients not met by commercial products. Soft chewable lozenges are compounded using a base of glycerinated gelatin; a mixture of glycerin, gelatin, and water that was adapted from the popular gelatin suppository based (20% gelatin, 70% glycerin, and 10% water).

Compounded Chewable Gummy Formulations and Bases

(selected list published in the International Journal of Pharmaceutical Compounding)

- Fentanyl 50-mcg Chewable Gummy Gels (Jan/Feb 2000)

- Lorazepam 1-mg Chewable Gummy Gels (Jan/Feb 2001)
- Fentanyl 50-mcg Chewable Gummy Gels (Mar/Apr 1998)
- Pediatric Chewable Gummy Gel Base (Mar/Apr 1997)
- Pediatric Chewable Gummy Gels (Mar/Apr 1997)

Despite their popularity and use, published drug dissolution and bioavailability studies are lacking in the literature. Dille et al. reported dissolution studies of a soft gelatin chewables containing either ibuprofen, acetaminophen, or meloxicam.[25] Results of each formulation showed drug release was comparable in dissolution studies when compared to standard tablet formulations of the same medication. The formulations also exhibited good drug stability for up to 24 months. Hattrem et al. conducted bioavailability studies of the ibuprofen chewable formulation and showed comparable bioavailable to the commercially available tablet dosage form.[26] This strongly suggests that the gelatin matrix of the formulation does not affect normal pharmacokinetics. The median time for peak serum concentrations reported after 3 chews and 8 chews were 1.25 and 1.75 hours, respectively. This was in comparison to a commercially available hard tablet at 1.5 hours. Since ibuprofen solubility is low (21 mg/L in water) the rate limiting step to absorption is drug dissolution. In contrast, midazolam HCl has high water solubility at low pH (>2 mg/mL in water) and will be readily absorbed. Therefore, the rate limiting step should be the dissolution of the gummy formulation. Our preliminary study shows complete dissolution of the gelatin gummies within 15 minutes. Additional information is provided in the Appendix A.

Bioavailability

The compounded gummy bears have a formulation intended to provide an environment of maximum drug solubility and release after ingestion. For example, the aqueous solubility of midazolam hydrochloride is greatest at low pH. More specifically, a pH below 4 would ensure adequate solubility for a formulation concentrated at 2 mg/mL.[27] Our gummy formulation base (with no drug) provides a low pH environment (pH 3.2, experimentally determined) with an organic acid buffering system of citric and malic acid. Additionally, the midazolam injection that is added to our base formulation during compounding has an adjusted pH 3. Since our gummies have a midazolam concentration of approximately 1.67 mg/mL there should be adequately soluble at the pH of the final formulations to ensure rapid dissolution and drug absorption. The formulation also contains other highly water-soluble components including sucrose (simple syrup) that rapidly dissolve in gastric juices and help form pores in the gummy that facilitate drug release and gelatin dissolution. Midazolam has also been reported to be absorbed transmucosal in the mouth from the buccal cavity[28], but with the limited residual time of the gummies in the mouth this is less significant.

In our case, the dissolution of the gelatin gummy and release of the drug can be considered the rate limiting step to oral absorption. Since midazolam is rapidly absorbed after oral administration[29], the faster the gelatin is dissolved the more rapid we should be drug absorption. Our gummy formulations have gelatin that is

already hydrated with water and further promotes an environment for fast dissolution of water-soluble drugs and the gelatin. The gelatin matrix used in the gummies have a so-gel transition temperature range of 28-31.5^{o}C, very much below physiologic conditions (37^{o}C), to promotes disintegration and dissolution during the start of mastication. The low melting temperature also allows quick dissolution in the gastrointestinal tract. Dissolution studies of fully intact gummy bear formulation demonstrated full drug release within 15 minutes. Chewing the gummy bear into pieces would be expected to enhance this rate. Further information regarding our studies are provided in the Appendix A.

Stability

A 14 day beyond-use date (expiry date) was placed for the compounded gummy preparations. This is based on USP <795> beyond-use dating for aqueous oral preparations in the absence of stability data. Since no direct stability studies have been performed on our compounded gummy formulation, we are relying on several studies that support our 14 days as being very conservative. These studies are listed below in figure 1. In summary, midazolam HCl injection is preserved and stable when diluted with various parenteral admixtures for over 14 days at room temperature and when subjected to high autoclaving temperatures (121^{o}C for 30 minutes). When midazolam HCl injection is compounded and mixed with oral liquids for ingestion, it was stable for 14 days (some up to 102 days) with no signs of microbial growth, color, turbidity, pH, or odor. When mixed with gelatin (Jell-O),

midazolam HCl was also shown to be stable for 14 days refrigerated, and 28 days when frozen.

SUMMARY OF PUBLISHED STABILITY STUDIES (MIDAZOLAM HCl)

PARENTERAL COMPOUNDED PREPARATIONS	
TITLE	SUMMARY
Chemical stability of midazolam injection by high performance liquid chromatography.	De Diego et al. [30] reported the stability of parenteral solutions of midazolam are very stable undiluted and when diluted in 5% dextrose even when exposed to light and room temperature conditions for over 14 days.
Photochemical decomposition of midazolam iv. Study of pH-dependent stability by high-performance liquid chromatography	Andersin et al.[31] reported Midazolam injection was also shown to be physically and chemically stable in the more complex aqueous environment of parenteral nutrition solutions for at least 5 hours; study did not evaluate stability past this time. Although solutions of midazolam are relatively stable, the lower the pH, the greater stability from photodegradation.
Extended stability of compounded preservative-free midazolam (as hydrochloride) injection	Trissel and Hassenbush[27] reported compounded midazolam solutions (2.5-5 mg/mL) in sodium chloride solutions (0.9%, 0.45%) were stable for three months when stored at 4,23, and 37 ^{o}C. Autoclaving the solution (121^{o}C for 30 minutes) showed little or no loss of midazolam content.
ORAL COMPOUNDED FORMULATIONS	
Stability of parenteral midazolam in an oral formulation	Walker et al. [32] The chemical and physical stability of an oral solution of midazolam made by mixing parenteral midazolam HCl solution with orange fruit flavored syrup was investigated using stability indicating methods. Results of this study showed solutions at a concentration of 0.35,0.64 and 1.03 mg/ml were stable and showed no appreciable degradation (<6.5%) at room temperature (23^{o}C) over a 102 day period (when the study ended). The syrup was packaged in polyethylene containers and prepared by adding 30 mL of distilled water to 50 mL of simple syrup and then adding 0.12 mL of pure orange extract with shaking. One drop each of red and yellow food coloring was added, and additional distilled water was incorporated to bring the volume to 100 mL. The midazolam hydrochloride injection was added to yield the test concentrations.
Stability of midazolam	Steedman et al. [33] The stability of an extemporaneously prepared 2.5-mg/mL solution of injectable midazolam

hydrochloride in a flavored, dye-free oral solution	HCl in a flavored dye-free syrup Syrpalta (1:1 ratio) was stable for 56 days at 7, 20, or 40 degrees C when stored in 1 oz amber glass bottles. There was also no visible signs of microbial growth, color, turbidity or odor observed through the same time period.
Making oral midazolam palatable for children	Peterson[34] Mixed midazolam injection in serpalata syrup, apple juice, and various carbonated beverage before settling on a concentrated grape Kool-Aid sweetened with Nutrasweet. More specifically, the concentrate was made by mixing a 2-quart package of Kool-Aid with 2 cups of water. The appropriate dose of midazolam (5 mg/mL injection) was then mixed with 5-10 mL of this concentrate. Driscoll Foundation Children's Hospital in Texas.
Stability of midazolam prepared for oral administration	Gregory et al. [35] The stability of midazolam HCl injection was investigated when mixed in syrup (Simple Syrup, NF) and flavored with peppermint oil to yield a concentration of 2.5 and 3 mg/mL. Results showed midazolam concentrations were minimally decreased and less than 10% loss for up to 14 days when stored in glass amber bottles at room temperature.
Stability of an oral midazolam solution for premedication in paediatric patients	Soy et al. [36] A extemporaneously prepared 1 mg/mL oral midazolam HCl solution was shown to be stable with no changes in pH for up to 60 days when stored at room temperature. The oral solution was made by mixing midazolam injection solution (5 mg/mL) with sodium saccharin, flavor drops (lemon or strawberry), and purified water. The oral solution contained 20 mL of midazolam hydrochloride (5 mg/mL), saccharin sodium 240 mg, lemon or strawberry flavor, and purified water 80 mL.
A palatable gelatin vehicle for midazolam and ketamine	Rosen and Rosen[19] suggested the liquid from a partially melted commercially available popsicle, orange juice, apple juice, cherry and banana flavor extracts, chocolate syrup, crème de marshino, and cola. The preferred vehicle in pediatric intensive care unit, operating room, and clinics at the University of Michigan Medical Center was flavored gelatin sweetened with sugar. Gelatin was made in ice cube trays prepared by adding 1.3 mL of gelatin to every 1 mL of drug. Cubes were made of 5, 10, or 15 mg and cut into proportions for fractional doses.
Stability of midazolam in	Geiger et al.[37] reported the stability of midazolam HCl oral suspension (1 mg/mL) prepared from the injection

SyrSpend SF and SyrSpend SF Cherry	and mixed with a commercial suspending and flavoring liquid combination (i.e., SyrSpend SF and SyrSpend SF Cherry). The suspension showed little to no loss on midazolam HCL content for 58 days when stored at ambient room temperature or refrigerated (2-8^{o}C) in low-actinic prescription bottles.
GUMMY (GELATIN) COMPOUNDED PREPARATIONS	
Stability of midazolam hydrochloride in extemporaneously prepared flavored gelatin	Bhatt-Mehta et al. [38] reported the stability of midazolam HCL in flavored gelatin (Jell-O; Kraft Foods) at a concentration of 1-2 mg/mL. No loss of midazolam was shown to occurred for samples stored under refrigeration (4^{o}C) at 14 days and stored frozen (-20^{o}C) for 28 days. The preparation was made by adding 30 or 90 mL of midazolam injection (5 mg/mL) to 120 mL to 135 mL of freshly prepared liquid gelatin for a 1-mg/mL or 2 mg/mL concentration. Additionally, no change in color or odor occurred, and no evidence of bacterial growth was observed. The liquid was then packaged in unit-dose cups containing 5 mg/5 mL and 15 mg/7.5 mL, respectively. The preparations were reported to be sweet but produced a bitter aftertaste that was more intense for the 2 mg/mL concentration.
Midazolam gelatin cubes for children	Allen LV reported[39,40] the preparation of midazolam in a gelatin base (Jell-O) prepared by adding 1 mL of midazolam injection (5 mg/mL) to 1.3 mL of a prepared gelatin solution and placing into ice-cube trays or other suitable molds. The gelatin base was prepared by mixing 6 Fl. oz of boiling water with a 3 oz package of flavored gelatin and allowed to cool before mixing with midazolam. A beyond use date of 14 days was provided based on USP; no other reference given.

Table 1. **Summary of Published Stability Studies (Midazolam HCL)**

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Appendix B

Pharmacology Experiments conducted by Dr. David Mastropietro

Sol-gel Temperature (Gummy Melting Temperature)

- Experimental Procedure: A 50 mL beaker with water and was placed in the center of a hotplate with an empty 25 mL beaker sitting inside it. A blank gummy (no drug) sample was placed into the 25 mL beaker and a digital thermometer rested inside. The temperature of the hotplate was increased slowly allowing equilibrium of temperature to the sample gummy. Temperature was recorded at the first visual sign of melting and again at complete melting of gummy. This temperature range served as the sol-gel transition range.
- Results: Onset of melting and free-flowing of the sample was initiated at 28^{o}C. Complete melting and loss of viscosity was seen at 31.5^{o}C

pH Test

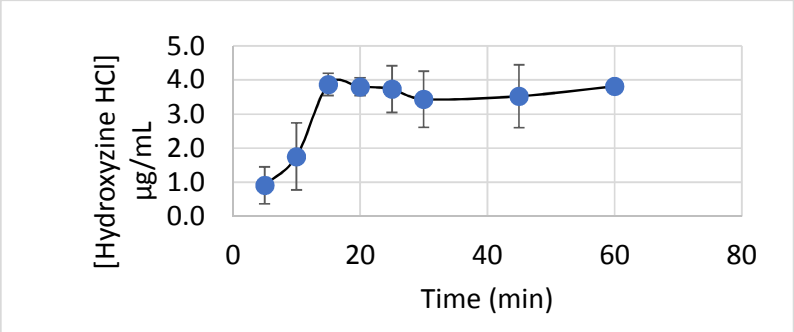
- Experimental Procedure: A blank gummy (no drug) sample weighing approximately 1.7-1.8 g was placed into a 25 mL beaker and 10 mL of distilled water was added. Under constant stirring the sample was heated to approximately 55^{o}C until all of the sample was dissolved. The solution was then allowed to cool to 25^{o}C before pH measurement was performed using a SympHony B10P benchtop meter.
- Results: Measurement of pH was performed at 25^{o}C with a stable reading of 3.20.

Dissolution Test

- Experimental Procedure: Compounded gummies containing 2.5 mg of hydroxyzine HCl were made and allowed to solidify for 6 hours under refrigeration. Based on compendial methods for hydroxyzine HCl tablets, gummies were then subjected to dissolution studies using a USP 2 Paddle method in 900 mL of distilled water at 37.^{o}C ±0.5^{o}C and a paddle rotational speed of 50 rpm. Hydroxyzine HCl concentration in the dissolution medium was analyzed over time. Aliquots withdrawn for analysis were replaced with equal volumes of fresh dissolution media at 37 °C. The concentration of hydroxyzine HCl in dissolution media was obtained using UV-Visible Spectroscopy on a PerkinElmer LAMBDA™ 365 instrument set at 230 nm. All extracts were passed through a 0.2 micron filter prior to analyses. To determine drug concentration, a calibration curve was constructed using drug solutions of known concentration. A linear calibration curve (absorbance against concentration) was obtained by plotting a minimum of 5 points covering the concentration range of interest and checked for linearity (r^2=0.999). Chemical interference from gelatin was observed with our testing method in the absorbance peak being measured resulting in slightly higher values being reported from our calibration curve in water. Reference samples containing dissolved blank gelatin gummy at equal

time points were therefore used as a baseline to minimize spectral overlap.

- Results: Dissolution data showed drug release occurred rapidly with the full dose being released within 15 minutes.



Dissolution of hydroxyzine HCl from compounded gummy bears

Appendix C

Compounding Procedures written by Dr. David Mastropietro

In addition to established quality standards of the pharmacy, the compounding record (CR) serves as the documentation ensuring the accuracy and completeness of each compounded preparation. According to USP <1168> written procedures should include details of the materials, equipment and procedures use that can be easily replicated. Records should also exit for compounding, packaging, storage.

A sample of the compounding record is in Appendix B.

In particular, the CR record for the gummy records:

- The compound name, strength, and amount prepared
- All ingredients, grades, and quantities used
    - Name, manufacturer, and lot number of each raw material used
        - This also provides ingredient tracking for any potential ingredient recalls
        - Certificates of Analysis are also reviewed for each bulk raw material
    - Name, strength, volume or quantity of each ingredient measured (2 person verified)
        - Ingredients used are stored in a clean dry area, adequately labeled, and handled using procedures to minimize and prevent contamination/cross-contamination
- Stability & Assignment of beyond-use-date (expiry date)
    - 14 days under refrigerated conditions [Based on USP <795> and published stability studies]
- Equipment
    - Document of equipment used in compounding
        - Both disposable and electromechanical
        - Prescription balance calibration verification is performed using standard weights after balance cleaning and prior to weight measurements.
- Calculations
- Preparatory procedures
    - Each step is standardized to ensure a consistent preparation that is reproducible
        - Descriptions include equipment used in the compounding process
- Packaging and Storage Requirements
    - Packaging is in a tight, light resistant amber prescription bottle container
        - Protects the preparation adequality from the environment and transport
- Quality Control (Final Check)

- According to the draft guidance of USP <1168> *Compounding for Phase I Investigational Studies,* the evaluation of one or more quality attributes (e.g., physical, chemical, and microbiological testing) should be performed before the investigational preparation is released. Compounded solid oral dosage forms can undergo physical QC tests to ensure the uniformity and accuracy of compounded preparations. These tests address individual dosage unit weights (including the average), total preparation weight, pH, and physical attributes such as appearance, taste, and smell.
    - For our compounded gummies, at the completion of compounding, physical characteristics (uniformity, clarity, odor, color, hardness) of the gummies are assessed to ensure they are consistent with those established. Additionally, the finished gummies are weighted to ensure they fall within ± 10% of the calculated individual dose weight.
    - The results of these quality control tests are documented as shown in the Compounding Record section.
    - Additionally, quality assurance (QA) measures are incorporated in the compounding process (i.e., weight measurements checked by 2 individuals) to ensure that the actual yield matches the theoretical yield of finished preparation. Any deviations will be accounted for, documented, and not dispensed.
    - A final check is also performed by a second Pharmacist employed by the pharmacy who reviews the compounding record to ensure the procedures and techniques used were faithfully followed and appropriately documented before dispensing on the order of the prescription.

Appendix D

Sample Compounding Record

RECORD INFORMATION		
Compounded Preparation Name: Midazolam 2.5 mg oral-chewable gummies		Date Compounded:
Total Quantity Compounded:	Pharmacist Signature:	Pharmacist Initials:
Rx#:	Patient Name:	

DEVICES & EQUIPMENT	
1. Electronic Balance	6. Beaker: 50-100 mL
2. Hot Plate and thermometer	7. Stir Rod
3. Gummy Bear mold: 1.486 mL	8. Mortar and Pestle: 1-2 oz
4. Weigh Boats/paper	9. Scoopula and Rubber Spatula
5. Oral Syringe(s)	10.

INGREDIENT TRACKING				
Ingredient Name	NDC	Manufacturer	Expiration	Lot
Gum Base (Gelatin)				
Citric Acid, USP (Anhydrous)				
Malic Acid, NF				
Syrup, NF (Simple)				
Sucralose				
Magnasweet®				
Bitterness Mask (Flavor Natural)				
Flavor				
Midazolam Injection (5 mg/mL) [as hydrochloride salt]				

INGREDIENT AMOUNTS						
Ingredient Name	QTY (1 mold = 1.5 mL)	Units	Multiplication Factor	Processing Error	QTY Measured	Qty Verified (initials)
Gum Base (Gelatin)	1.1	g				
Citric Acid, USP (Anhydrous)	0.025	g				
Malic Acid, NF	0.025	g				
Syrup, NF (Simple) [1.313 g/mL]	0.1 (0.1313 g)	mL				
Sucralose	0.030	g				
Magnasweet®	0.0005	g				
Bitterness Mask (Flavor Natural) [exp density---assuming 5 gtts=39.25 as below	2 0.006	drops mL				
Flavor (12 drops =0.036 mL from 21'needle) [exp.density 5 gtts=39.25 mg]	5 0.015	drops mL				
Midazolam Injection (5 mg/mL) [as HCl salt]	0.5	mL				

COMPOUNDING PROCEDURE STEPS

1. Clean workstation/ verify balance calibration
2. Determine the weight requirements for all ingredients employing a processing error or extra gummy
3. Weigh, and then melt required amount of Gum Base (Gelatin) on hotplate in a 50-mL beaker; Temperature range 60°C–65°C.
4. Weigh, and then triturate Citric Acid, Malic Acid together, then Sucralose, and Magnasweet using mortar and pestle to form a fine homogenous powder
5. Draw up and eject syrup into mortar containing triturated powder blend and mix to form a homogenous slurry
6. Draw up and eject midazolam injection into the uniform slurry from step#5 and stir until homogenous
7. Add slurry to melted Gum Base off the hotplate. Stir with glass stir-rod until uniform consistency
8. Pour final mixture into molds, allow slight overfilling. Allow mixture to solidify at room temperature before placing in fridge.
9. Remove refrigerated gummies from mold and perform all quality assessment procedures. Store gummies in refrigerator.
10. Clean workstation

CALCULATIONS

Define Calculation	Volume Needed to be occupied by Gummy Base
Show Work	**Per 1 Mold** **Mold Volume: 1.500 mL** - Midazolam: 0.500 mL - Flavor Drops: 0.015 mL [20 drops =0.06 mL) - Simple Syrup 0.1 mL - Bitterness Sup. 0.006 mL - Powders Disp. 0.06 mL **0.819 mL** (assuming 1:1 volume)
Define Calculation	Amount of Sweetened Gummy Base needed per 1 Mold
Show Work	Density of gummy base is 1.334 g/mL . The amount of base needed to fill the remaining 0.819 mL is below $\left(\frac{1.334\ g}{1\ mL}\right)\ x\ 0.819\ mL = 1.09$ g of gelatin base/ 1 gummy ≈1.1 g/gummy

4) LABELING, PACKAGING, AND STORAGE INFORMATION

Directions for Use:

Chew and then swallow one gummy at a time as directed

Storage Requirements:	BUD:
Can be stored under refrigeration. Keep away from moisture and light	Not later than 14 days when storied at controlled cold temperatures. *(As defined by USP 795 Standards for Water-Containing oral Formulations)*

Packaging:

Tight, light-resistant container (e.g. prescription vial)

Auxiliary Labeling:

Protect from heat and moisture. Store in refrigerator.

Patient/Caregiver/Staff Instructions:

Chew and then swallow. Keep in safe place, not to be confused with candy

5) QUALITY ASSURANCE TESTING

Finished Product Description:

Clear and semi-firm gummy with slight fruit odor and light red/pink color

Quality Assurance/Assessment:

Select at least 5 gummies and determine the weight variation is of the calculated theoretical value

Theoretical weight of one gummy:	Max permissible weight:	Min permissible weight:

	Actual Weight	Percent Deviation	Pass Fail
1			
2			
3			
4			
5			

Appendix E

Pre- Sedation Checklist

NOVA SOUTHEASTERN UNIVERSITY
College of Dental Medicine

PEDIATRIC DENTISTRY

PRESEDATION CHECK LIST

Date_____

Patient: _____Chart_____ __M __F

Age: ____yr. Weight: _____lb_____Kg (is BMI over 85%?)

Indication for sedation: (check all that apply)

- o Fearful/anxious patient for whom basic behavior guidance techniques have not been successful
- o Patient unable to cooperate due to lack of psychological or emotional maturity and/or mental, physical, or medical disability
- o To protect patient's developing psyche
- o To reduce patient's medical risk

Medical history/review of systems (ROS)- Describe positive findings: (check all that apply)

- o Allergies &/or previous adverse drug reactions
- o Current medications (including OTC)
- o Relevant diseases, physical/neurologic impairment
- o Previous sedation/general anesthetics
- o Snoring, obstructive sleep apnea, mouth breathing
- o Other significant findings (eg, family history)

Description:_____

_____

ASA classification: I II III* IV* E

*Medical consultation indicated? NO_____ YES_____

Date requested: _____

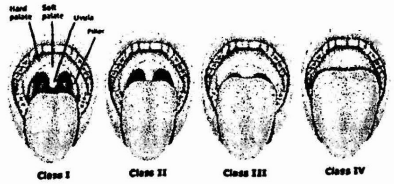
Comments_____

_____

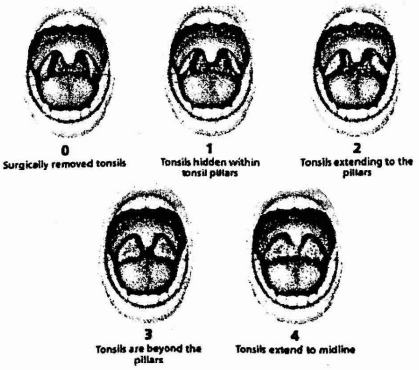
_____

Airway Assessment:

- o Obesity
- o Limited neck mobility
- o Micro/retrognathia
- o Macroglossia
- o Mallampati Scale I II III IV



o Brodsky Scale 0 1 2 3 4



Is this patient a candidate for in-office sedation? YES_____ NO_____

Pediatrician/Physician contact information: Name:_____ Telephone #:_____

Address:_____

Faculty Signature_____Date_____

Informed consent: **Resident name who reviewed with parent/guardian**

Consent for sedation _____

Consent for N_2O _____

Consent for Protective Stabilization _____

Consent for extractions _____

Appendix F

Sedation Record

NOVA SOUTHEASTERN UNIVERSITY
College of Dental Medicine

Pediatric Dentistry Sedation Record

Date: _____

Patient: _____ Chart #_____ ❑ M ❑F Age: ___yr Weight: _____lb_____kg

Indication for sedation: ❑ Fearful/anxious patient for whom basic behavior guidance techniques have not been successful
❑ Patient unable to cooperate due to lack of psychological or emotional maturity and/or mental, physical, or medical disability
❑ To protect patient's developing psyche
❑ To reduce patient's medical risk

Medical history/review of systems (ROS)	NONE	YES*	Describe positive findings:
Allergies &/or previous adverse drug reactions	❑	❑	_____
Current medications (including OTC)	❑	❑	_____
Relevant diseases, physical/neurologic impairment	❑	❑	_____
Previous sedation/general anesthetics	❑	❑	_____
Snoring, obstructive sleep apnea, mouth breathing	❑	❑	_____
Other significant findings (eg, family history)	❑	❑	_____

Airway Assessment	NO	YES*
Obesity (BMI must be < 85%)	❑	❑
Limited neck mobility	❑	❑
Micro/retrognathia	❑	❑
Macroglossia	❑	❑

Mallampati Scale I ❑ II ❑ III ❑ IV ❑
Brodsky Scale I ❑ II ❑III ❑ IV ❑

ASA classification: ❑ I ❑ II ❑ III* ❑ IV* ❑ E * Medical consultation indicated? ❑ NO ❑ YES Date requested: _____
Comments: _____

Is this patient a candidate for in-office sedation? ❑ YES ❑ NO Faculty's signature: _____

Plan

	Name/relation to patient	Date	by Resident
Informed consent obtained from			
Pre-op instructions reviewed with			
Post-op precautions reviewed with			

Assessment on Day of Sedation

Accompanied by: _____ Relationship(s) to patient: _____

Medical Hx & ROS update	NO	YES	NPO status	Airway assessment	NO	YES	Checklist
Change in medical hx/ROS	❑	❑	No liquids&/or foods since _____	Upper airway clear	❑	❑	❑ Appropriate transportation home
Change in medications	❑	❑		Lungs clear	❑	❑	❑ Monitors functioning
Recent respiratory illness	❑	❑		Mallampati Scale I ❑ II ❑ III ❑ IV ❑			❑ Emergency kit, suction, & O_2 available
				Brodsky Airway I ❑ II ❑ III ❑ IV ❑			

Vital signs (If unable to obtain, check ❑and document reason: _____)
Blood pressure: _____/_____ mmHg Heart Rate: _____/min SpO_2:_____%
Comments: _____

Presedation cooperation level: ❑Unable/unwilling to cooperate ❑Rarely follows requests ❑Cooperates with prompting ❑Cooperates freely
Behavioral interaction: ❑Definitively shy and withdrawn ❑Somewhat shy ❑ Approachable
Guardian was provided an opportunity to ask questions, appeared to understand, and reaffirmed consent for sedation? ❑ YES ❑ NO

Drug Dosage Calculations

Sedatives
Agent _____ Route _____ _____mg/kg X _____kg = _____mg ÷ _____mg/mL = _____mL
Agent _____ Route _____ _____mg/kg X _____kg = _____mg ÷ _____mg/mL = _____mL
Agent _____ Route _____ _____mg/kg X _____kg = _____mg ÷ _____mg/mL = _____mL

Emergency reversal agents
For narcotic: NALOXONE IV, IM, or subQ Dose: 0.1 mg/kg X _____kg = _____mg (Maximum dose: 2 mg; may repeat after 2-3 min)
For benzodiazepine: FLUMAZENIL IV, IM Dose: 0.01 mg/kg X _____ kg = _____mg = _____ml (Maximum dose: 0.2 mg=2 ml; may repeat up to 4 times)

Local anesthetics (maximum dosage based on weight)

Lidocaine 2%	(34 mg/ 1.7 mL cartridge)	4.4 mg/kg X	_____kg = _____mg	(not to exceed 300 mg total dose) =_____cartridge/s
Articaine 4%	(68 mg/ 1.7 mL car tridge)	7 mg/kg X	_____kg = _____mg	(not to exceed 500 mg total dose)=_____cartridge/s
Mepivacaine 3%	(51 mg/ 1.7 mL cartridge)	4.4 mg/kg X	_____kg = _____mg	(not to exceed 300 mg total dose)=_____cartridge/s
Prilocaine 4%	(68 mg/ 1.7 mL cartridge)	6 mg/kg X	_____kg = _____mg	(not to exceed 400 mg total dose)=_____cartridge/s
Bupivacaine 0.5%	(8.5 mg/ 1.7 mL cartridge)	1.3 mg/kg X	_____kg = _____mg	(not to exceed 90 mg total dose) =_____cartridge/s

Intraoperative Management and Post-Operative Monitoring

EMS telephone number: 9-911

Monitors: ❑ Pulse oximeter ❑ Precordial/pretracheal stethoscope ❑ Blood pressure cuff ❑ Capnograph ❑ Rubber dam/Isodry

Protective stabilization/devices: ❑ Papoose ❑ Neck/shoulder roll ❑ Manual hold ❑ Mouth prop

TIME	Baseline :	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
Sedatives[1]																						
N_2O/O_2 (%)																						
Local[2] (mg)																						
SpO_2																						
Pulse																						
BP																						
CO_2																						
Papoose																						
Procedure[3]																						
Sedation level*																						
Behavior*																						
Comments[4]																						

1. Agent _____ Route _____ Dose _____ Time _____ Given by _____ Administration 1 2 3
   Agent _____ Route _____ Dose _____ Time _____ Given by _____ Administration 1 2 3

Faces Scale 1 2 3 4 5
Faces Scale 1 2 3 4 5

1=didn't take at all
2=partially took it
3= took it

2. Local anesthetic agent/s ❑ Topical ❑ Local ____carpules of ❑ 2% lido with 1:100K epi ❑ 4% septo ❑ other_____
3. Record dental procedure start and completion times, transfer to recovery area, etc.
4. Enter letter on chart and corresponding comments (eg, complications/side effects, airway intervention, reversal agent, analgesic) below:

A. _____ D. _____
B. _____ E. _____
C. _____ F. _____

Sedation level*

None (typical response/ cooperation for this patient)
Mild (anxiolysis)
Moderate (purposeful response to verbal commands; light tactile sensation)
Deep (purposeful response after repeated verbal or painful stimulation)
General Anesthesia (not arousable)

Behavior/ responsiveness to treatment†

Excellent: quiet and cooperative
Good: mild objections&/or whimpering but treatment not interrupted
Fair: crying with minimal disruption to treatment
Poor: struggling that interfered with operative procedures
Prohibitive: active resistance and crying; treatment cannot be rendered

Overall effectiveness: ❑ Ineffective ❑ Effective ❑ Very effective ❑ Overly sedated

Additional comments/treatment accomplished: _____

Discharge

Criteria for discharge

- ❑ Cardiovascular function is satisfactory and stable.
- ❑ Airway patency is satisfactory and stable.
- ❑ Patient is easily arousable.
- ❑ Responsiveness is at or very near presedation level (especially if very young or special needs child incapable of the usually expected responses).
- ❑ Protective reflexes are intact.
- ❑ Patient can talk (return to presedation level).
- ❑ Patient can sit up unaided (return to presedation level).
- ❑ State of hydration is adequate.

Discharge vital signs

Pulse: _____/ min
SpO_2: _____%
BP: _____/_____ mmHg

Discharge process

❑ Post-operative instructions reviewed with _____ by _____

❑ Transportation ❑ Airway protection/observation ❑ Activity ❑ Diet ❑ Nausea/vomiting ❑ Fever ❑ Rx ❑ Anesthetized tissues
❑ Dental treatment rendered ❑ Pain ❑ Bleeding ❑ _____ ❑ Emergency contact

❑ Next appointment on: _____ for _____

I have received and understand these discharge instructions. The patient is discharged into my care at _____ ❑ AM ❑ PM

Signature: _____ Relationship: _____ After hours number: _____

Resident Operator
Printed name: _____

Resident Observer/s
Printed name/s: _____

Faculty Signature & _____
Printed name: _____