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Morphine Revisited in Pediatric Dentistry: A Retrospective Study of
Morphine + Hydroxyzine + Ibuprofen

by

Adam Shaffer, DDS

THESIS

Submitted in partial satisfaction of the requirements for the degree of

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Morphine Revisited in Pediatric Dentistry. A Retrospective Study of a Moderate Sedation Regimen of Morphine + Hydroxyzine + Ibuprofen

Adam Shaffer, DDS

Abstract

Purpose: The purpose was to evaluate the safety and efficacy of a moderate sedation drug regimen consisting of P.O. morphine (0.66 mg/kg, up to a maximum of 30 mg), hydroxyzine (25 mg flat dose), and ibuprofen (100 mg flat dose), as utilized with nitrous oxide and oxygen sedation.

Methods: A convenience sample of 595 sedation records were retrieved from one group of dentists all utilizing the same protocols. The sedation records were chronologically screened and those meeting inclusion and exclusion criteria were subsequently analyzed for descriptive data, oxygen saturation, cardiovascular stability, behavioral data, and adverse events.

Results: Of the original sample of 595 sedation records, 360 (60.5%) met inclusion and exclusion criteria for further analysis. Of the 360 records analyzed, the distribution of males and females was roughly equal (49.4% male, 50.6% female), with a median age of 5.0 years (range: 2.0 years to 11.8 years) and a median weight of 18.6 kg (range 9.5 kg to 43.18 kg). The median wait time was 63 minutes, and the median working time was 70 minutes. Asymptomatic hypotension occurred in 18 of 340 records (5.3%); asymptomatic tachycardia occurred in 20 of 327 records (6.1%), and asymptomatic bradycardia occurred in 14 of 349 records (4.3%). Sedated patients were quiet 72.1% of the time, crying 13.4% of the time, struggling 6.0% of the time, sleeping 4.0% of the time, and engaging in other behaviors 4.6% of the time. Significant adverse events

occurred in 5 of 360 records (1.4%), with a true desaturation event occurring in one sedation record ($\text{SpO}_2=87$), prolonged or excess sedation occurring in three sedation records, and intraoperative nausea/vomiting occurring in one sedation record.

Conclusions: The results suggest morphine may serve as a viable opiate in P.O. moderate sedation regimens in pediatric dentistry.

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1. INTRODUCTION

Management of the uncooperative, fearful, and/or special needs child continues to be one of the most challenging aspects of pediatric dental practice. While many of these children can be managed using basic behavior guidance techniques, the American Academy of Pediatric Dentistry (AAPD) recognizes the usefulness of advanced behavior guidance techniques, including protective stabilization, sedation, and general anesthesia.¹

A survey of active members of the AAPD conducted in 2000 revealed that sedation continues to be frequently utilized, especially among selected practitioners who use sedative regimens frequently in their practices.² Similarly, a recent survey sent to members of the International Association of Pediatric Dentistry (IAPD) and the European Academy of Pediatric Dentistry (EAPD) revealed that advanced behavior guidance techniques remain widely used in facilitating the dental treatment of children: 44% of respondents reported using oral sedation in their practices, and 52% reported using general anesthesia.³

Guidelines for behavior guidance strategies, including the use of advanced behavior guidance techniques and sedation, have been established by the American Academy of Pediatric Dentistry.⁴⁻⁶ These guidelines do not explicitly discuss the advantages and disadvantages of specific drug regimens,⁴⁻⁶ however, and numerous

publications in both the dental and medical literature express the need for increased research in the realm of pediatric sedation. As Cravero and Blike write: “Sedating children for diagnostic procedures has engendered debate both within and between the myriad of pediatric specialists who provide this service. In hospitals across the United States, there is little agreement as to which medications, techniques, practice settings, or even personnel should be involved in its delivery.”⁷ In this retrospective study, the safety and efficacy of a drug regimen utilizing morphine as a primary component, and administered orally by pediatric dentists in a private practice setting, is evaluated.

2. BACKGROUND AND SIGNIFICANCE

2.1 Moderate Sedation in Pediatric Dentistry

The AAPD states: “The goals of sedation in the pediatric patient for diagnostic and therapeutic procedures are: 1) to guard the patient’s safety and welfare; 2) to minimize physical discomfort and pain; 3) to control anxiety, minimize psychological trauma, and maximize the potential for amnesia; 4) to control behavior and/or movement so as to allow the safe completion of the procedure; and 5) to return the patient to a state in which safe discharge from medical supervision, as determined by recognized criteria is possible”. It should be noted, however, that the term “sedation” represents a range of physical and psychological states on the overall spectrum of pain and anxiety control.⁸

Sedation can occur through many different routes. Various states of sedation can be achieved by means of iatrosedation (defined as “the relief of anxiety through the dentist’s behavior”), hypnosis, and various routes of drug administration: oral, rectal, topical, sublingual, intranasal, transdermal, subcutaneous, intramuscular, inhalation

(pulmonary) and/or intravenous.⁸ Depending on which modalities of sedation are chosen, and the extent to which they are utilized, patients can be brought to one of three widely recognized states of sedation: 1) minimum sedation, 2) moderate sedation, or 3) deep sedation.⁹

The second of these, moderate sedation (also commonly referred to as “conscious sedation”, “sedation/analgesia”, or when achieved via the oral route, “oral conscious sedation”), is the target level of sedation for many P.O. sedation regimens utilized by pediatric dentists when treating apprehensive or uncooperative children and/or special needs patients.

There are currently only a limited number of drug regimens that are routinely employed by pediatric dentists for the purposes of sedation.² The aforementioned survey of active members of the AAPD, conducted by Milton Houpt, DDS, PhD in 2000, reveals that certain, specified drugs, including antihistamines (e.g. hydroxyzine, promethazine), benzodiazepines (e.g. diazepam, midazolam), narcotics (e.g. meperidine), and nonbarbiturate sedative-hypnotics (e.g. chloral hydrate), are frequently utilized by pediatric dentists as oral sedative medications – either alone or in combination. These oral medications are then typically supplemented with nitrous oxide and oxygen inhalation sedation.²

While this survey provided much information on commonly used sedative drugs and drug combinations, it failed to acknowledge the small, but significant, percentage of sedations where lesser used sedative drugs and/or drug combinations are employed.² A more recent survey of program directors and students of advanced pediatric dentistry training programs in the United States revealed that additional drugs are being utilized

and taught as well.¹⁰ These include the benzodiazepines, triazolam and lorazepam, the narcotics morphine and fentanyl, and the NMDA receptor antagonist/dissociative anesthetic ketamine.¹⁰ Additional research on these “lesser used” sedative drugs and drug combinations, within the context of being used for the purposes of sedation in pediatric dentistry, is warranted.

2.2 Meperidine in the Dental and Medical Literature

Meperidine use in pediatric dentistry has been well documented, and has historically been the opiate of choice in pediatric dentistry for the purposes of P.O. moderate sedation.^{2, 11-18} Indeed, most articles in the dental literature have reported generally favorable results in regards to the safety and efficacy of drug regimens including meperidine as a component.^{2, 11-18}

However, while meperidine continues to be utilized and accepted within the dental community, many clinicians and professionals outside the dental community have become increasingly critical of meperidine’s role in providing safe analgesia and sedation.¹⁹⁻²³ As Marcia L. Buck relates in *Journal of Pediatric Pharmacology and Therapeutics*: “...there is now substantial evidence that meperidine provides no greater analgesia or antispasmodic effect than other opioids. Over the past quarter century, a growing number of case reports and clinical studies describing meperidine’s adverse effects have changed opinion on the role of this drug in clinical practice.”²² Notably, while many of the criticisms about meperidine from outside the dental community are particularly significant in regards to long-term use of the drug, other criticisms are

significant even at dosages commonly utilized for the purposes of sedation in pediatric dentistry.¹⁹⁻²³

Many of the disadvantages related to using meperidine, as compared to other opioid drugs, are related to the breakdown of meperidine to the active metabolite normeperidine. Meperidine is unique in that it is metabolized by two different pathways: 1) Carboxylesterase metabolism to meperidinic acid, an inactive metabolite, and 2) N-demethylation by the hepatic cytochrome P-450 system to normeperidine, a non-opioid active metabolite.²⁰ The production of normeperidine is undesirable, and represents additional potential risk to the patient.²⁰ As Latta et al. explains: “The active nonopioid neurotoxic metabolite normeperidine has half the analgesic potency of meperidine but two to three times the potency as a central nervous system (CNS) excitatory agent. An overlooked clinical iatrogenic event is the propensity of normeperidine to precipitate anxiety, hyperreflexia, myoclonus, seizures and mood changes within 24 hours.”²⁰

Normeperidine also has a longer half-life than meperidine, and has been reported to accumulate in “patients with renal dysfunction, patients receiving large doses, or patients receiving extended therapy (greater than 24 to 48 hours) ... [although] reports of toxicity do exist in patients with normal renal function and in patients receiving an approved dose.”²³ Similar concerns about normeperidine have been expressed by Koczmara, et al.: “Normeperidine toxicity is often under-recognized. Doses as low as 260 mg per day have been reported to cause grand mal seizures and doses as low as 46 mg per day have been reported to elicit muscle twitches or tremors, suggesting a wide variability and unpredictability of patient responses.”¹⁹ It is not uncommon for dosages of 50 mg or more to be utilized for P.O. moderate sedation in pediatric dentistry.

Normeperidine additionally has an extended half-life elimination: “The $T_{1/2\beta}$ elimination half-life of normeperidine was found to be anywhere from 14-21 to 24-48 hours.”²⁰ Signs and symptoms associated with normeperidine toxicity include irritability, agitation, tremors, tachycardia, muscle twitches, hypertension, disorientation, and even grand mal seizures.¹⁹ Interestingly, while naloxone is an effective reversal agent for meperidine, deleterious effects of normeperidine such as CNS excitation and generalized seizures are not effectively antagonized by naloxone.²⁴

Meperidine is also known to have a relatively low analgesic potency, as compared to morphine, and has been reported in the literature to have an equal or greater propensity for respiratory depression at equianalgesic doses. For example, in *Pharmacology and Therapeutics for Dentistry*, Gerald F. Gebhart writes: “Meperidine is approximately one eighth to one tenth as potent as morphine; when given parenterally at equianalgesic doses, the degree of sedation and respiratory depression is the same for both drugs.”²⁵ Lewis et al., and Latta et al. refute the latter of these claims, however, and suggest that meperidine possesses a greater propensity for respiratory depression at equianalgesic doses.^{20, 26} More specifically, Lewis et al. states that the “respiratory depressant effects of meperidine are perhaps more prevalent than with morphine.”²⁶ Latta et al. similarly reports: “Even at twice the equipotent dose of morphine compared with meperidine, the respiratory depressant effect of meperidine exceeded that of morphine.”²⁰

Meperidine possesses additional characteristics that render it unique among the opiate drugs as well. For example, patients receiving monoamine oxidase inhibitors (MAOIs) and/or certain serotonin reuptake inhibitors should avoid meperidine due to

high risk of drug interactions that can lead to the potentially fatal serotonin syndrome.^{19,}

²³ In this reaction, the re-uptake of serotonin is inhibited, and the presentation of “mental status changes, myoclonus, muscle rigidity, tremors, diaphoresis, and hyper-reflexia,” is very similar to the presentation of normeperidine toxicity. While it may not be common for many pediatric patients to be taking MAOIs or serotonin reuptake inhibitors, the significant dangers to those patients who do take them remain: “Fatal outcomes due to serotonin syndrome have occurred when even a single dose of a monoamine oxidase inhibitor was ingested within 14 days of meperidine administration.”¹⁹

Meperidine can also be characterized as exhibiting greater histamine release than morphine or fentanyl when given at equipotent doses,²⁴ a side-effect contributing to symptoms such as itching.

It should additionally be noted that studies have been published suggesting meperidine may be more likely to cause nausea and/or vomiting than morphine.²⁷ For example, in a study published by Silverman, et al., parenteral meperidine was more likely to cause nausea and/or vomiting than morphine: “Our data noted a significant difference in the prevalence of nausea and vomiting with the use of morphine vs. meperidine. Those who received meperidine reported nausea or vomiting 12.82% of the time, compared with the morphine group who had a zero prevalence of nausea or vomiting, a statistically significant difference.”²⁷ It should be noted, however, that other sources give more conservative estimates of gastrointestinal disturbances, including nausea or constipation, after oral meperidine use, as occurring in approximately five percent of patients.²⁸

Meperidine is “the preferred opiate (56% versus 38% morphine) among addicted physicians.”²⁰ While the reason for this remains unknown, investigators such as Walker and Zacny have stated that meperidine had the most intoxicating and intense effects of all the narcotics tested;²⁹ however, these effects were short lived, lasting approximately five minutes.^{20, 29}

An important consideration when discussing meperidine use in dentistry and medicine is the current trend in the medical community of reducing or eliminating meperidine use. As Daniel et al. writes: ‘Because meperidine is dangerous for patients who are elderly, have renal insufficiency, and take certain medications (e.g. monooxidase inhibitors), some facilities have taken steps to decrease or completely eliminate its use.’³⁰ Similarly, Latta et al. states:

Meperidine use has a narrow place in therapy, if any, for interventional pain owing to procedures... The Joint Commission on Accreditation of Health Care Organizations has taken steps to discourage the use of meperidine in the implementation of its new pain guidelines. Many health organizations have severely restricted its availability or removed it from the formulary. One of the negative markers looked at by skilled nursing facilities in their reviews is the use of meperidine. ... There are many options that are considerably better although clinicians may not be as familiar with their use.²⁰

While these guidelines are heavily influenced by the negative aspects of meperidine use in the elderly, in medically compromised patients, and for patients requiring long-term care, certain aforementioned negative aspects of meperidine remain. Furthermore, restrictions of meperidine in hospital formularies will inevitably influence pediatric dentists working in hospital settings.

Given the limited utilization of narcotic drug regimens in pediatric dentistry that do not include meperidine, in conjunction with the increasing criticism of meperidine by

the medical community, increased research for alternative narcotic drug regimens in P.O. moderate sedation drug regimens in pediatric dentistry is warranted.

2.3 Morphine in the Dental and Medical Literature

Currently, only two studies exist in the dental literature regarding morphine use in moderate sedation drug regimens for the purposes of facilitating pediatric dentistry. Neither of these studies address the specific drug regimen being examined in this study, namely morphine (0.66 mg/kg, up to a maximum of 30 mg), hydroxyzine (25 mg flat dose), and ibuprofen (100 mg flat dose), utilized concurrently with 30-50% nitrous oxide and 50-70% oxygen.

The first study evaluating morphine use in moderate sedation drug regimens was published in 1986 by Howard S. Schneider in *Pediatric Dentistry*.³¹ This study was retrospective over a nine year period, and examined the clinical effects of using morphine sulfate and hydroxyzine pamoate for sedating the apprehensive child for dental procedures.³¹ Despite a very large sample size of 4363 patients (convenience sample), the study had numerous limitations, including: “(1) not recording the percentage of nitrous oxide to oxygen used; (2) not recording the amount of lidocaine hydrochloride used; (3) not recording the number of cases of vomiting; (4) not using a pulse oximeter to record oxygen level in the blood; and (5) not classifying the depth of sedation for each patient.”³¹ Nonetheless, it was the investigator’s opinion that: “The state of euphoria [when using morphine sulfate] is much greater than that resulting from meperidine hydrochloride and alphaprodine hydrochloride.”³¹ Ultimately, the conclusions derived by the investigator were simply that: “Morphine sulfate should be

considered as an alternative to meperidine hydrochloride and alphaprodine hydrochloride for sedation of the child patient in dentistry. The results were satisfactory within defined parameters.”³¹

The second study evaluating morphine use in moderate sedation drug regimens was published in 1992 by Susan Merlene Roberts, et al., also in *Pediatric Dentistry*.³² In this study, two submucosal/oral sedation regimens were compared.³² One group of patients (Group A) utilized submucosal morphine (0.15 mg/kg) and oral promethazine (1.1 mg/kg).³² Another group of patients (Group B) utilized oral meperidine (2.2 mg/kg) and oral promethazine (1.1 mg/kg).³² Among the conclusions made by the investigators were the conclusions that: “...3. There were no statistically significant differences in the effectiveness of the two sedation regimens studied with respect to modifying the behavior of the moderately uncooperative pediatric dental patient... [and] 5. The physiologic parameters of hemoglobin oxygen saturation, respiratory rate, and blood pressure did not change significantly at any interval for either of the sedation regimens studied.”³²

As stated previously, oral morphine continues to be widely used in the medical community, and is considered to be the “drug of first choice” in certain clinical situations,³³ in part due to its long history of use, numerous available research studies, and significant clinical track record.^{33, 34} In the article entitled *Clinical Pharmacokinetics of Morphine*, Ralph A. Lugo and Steven E. Kern state: “Morphine is the most widely used opioid analgesic for acute and chronic pain and is the standard against which new analgesics are measured.”³⁵

Additionally, while morphine use has historically been avoided due, in part, to misconceptions that “it is unsafe to administer opioids to children, and that children often suffer respiratory depression following administration of morphine”³⁶, Kart et al. state that “morphine can be considered safe to use in neonates, infants, and children.”³⁷

Nonetheless, morphine does have a number of side effects: “The most common side effects of morphine include nausea and vomiting, sedation, pruritis, and urinary retention. Other possible side effects are constipation, broncho-constriction, respiratory depression, myoclonic movement and physical and psychological dependence.”³⁷ However, it should be noted that, while the “side effects described in children are similar to those observed in adults... It has not been completely documented whether the susceptibility and incidence of side effects is comparable for the different age groups.”³⁷ The authors of this publication have not found published guidelines or recommendations for the optimal dosages of P.O. morphine for the purposes of moderate sedation in pediatric dentistry, either alone or in combination.

2.4 Hydroxyzine in the Dental and Medical Literature

Hydroxyzine is a commonly employed medication for purposes of sedation in pediatric dentistry, and is well documented in the literature^{8, 25, 2, 11, 38, 39}. It is a medication commonly utilized in conjunction with drugs such as chloral hydrate, meperidine, and/or midazolam.^{2, 38} As a first-generation H₁ antihistamine, hydroxyzine produces mild CNS depression, as well as has anticholinergic, antihistaminic, and antiemetic effects.²⁵ Notably, hydroxyzine additionally produces mild cardiovascular

depression and respiratory depression, has antiarrhythmic properties, and may cause bronchodilation.²⁵

When combined with opiates such as morphine, hydroxyzine reduces opiate-induced nausea and vomiting, and produces greater sedation and analgesia than an opiate alone.^{8, 25} Accordingly, some authors have even suggested that CNS depressant drugs should have their dosages reduced when used in combination with hydroxyzine due to fears of potentiation.²⁵

Optimal dosages of P.O. hydroxyzine have not been unequivocally demonstrated. As Faytrouny et al. report: "...dosages and schedules for oral administration of hydroxyzine have varied widely in clinical reports, ranging from 20 to 60 mg taken 45 min to 1 h before treatment."³⁸ Additionally, some authors report improved efficacy of hydroxyzine when used in combination with nitrous oxide,⁴⁰ while others recommend dosages based on weight (e.g. 3.7 mg/kg).^{40, 41}

2.5 Ibuprofen in the Dental and Medical Literature

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that is "one of the most widely used analgesic-antipyretic-anti-inflammatory drugs today".⁴² It has an extremely low incidence of morbidity or mortality associated with its use.⁴² Generally considered a very safe medication, and described by some as "the mildest NSAID with the fewest side effects..."⁴², safety concerns regarding ibuprofen use are most often related to "very rare but serious adverse reactions" such as Stevens-Johnson syndrome, renal or hepatic failure, or necrotizing fasciitis, as well as cardiovascular conditions and cardio-renal symptoms that are more commonly linked to other NSAIDs.⁴²

Ibuprofen can be utilized either preoperatively or postoperatively in dentistry for the purposes of relief from postoperative pain.^{25, 43-48} The efficacy of administering analgesics such as ibuprofen preoperatively has been questioned by some authors, however, and more studies on this practice are needed. As Dean et al., discuss in *McDonald and Avery's Dentistry for the Child and Adolescent*, administering ibuprofen preoperatively is “not without controversy... and there are conflicting reports within the literature as to the efficacy of this technique.”⁴³ For instance, Baygin et al. report a reduction of pain scores in patients who received pre-emptive dosages of ibuprofen prior to primary tooth extraction(s), and recommend consideration of pre-emptive analgesics in children before extractions.⁴⁶ Conversely, Aznar-Arasa et al., failed to show a significant reduction in pain, facial swelling, or trismus after lower third molar extraction, when ibuprofen was given preoperatively versus postoperatively. Given such disparities in the literature, a consensus on the efficacy of preoperative administration of ibuprofen prior to invasive dental treatment has not yet been achieved.

Notably, when utilized for management of postoperative pain, recommended pediatric dosages for ibuprofen are 4-10 mg/kg/dose given at 6- to 8- hour intervals.⁴³

2.6 Nitrous Oxide in the Dental and Medical Literature

Nitrous oxide, a “colorless, nonirritating gas with a pleasant, mild odor and taste”,²⁵ has been used as an anesthetic in dentistry and medicine since the early 1840s,⁴⁹ It is known to have analgesic, anxiolytic, and mild sedative effects when used at concentrations commonly utilized in dentistry.⁴⁹ Similarly, the American Academy of Pediatric Dentistry reports that nitrous oxide “is an effective analgesic/anxiolytic agent

causing central nervous system (CNS) depression and euphoria with little effect on the respiratory system.”⁵⁰

Many sources have illustrated the frequency of use of nitrous oxide and oxygen inhalation sedation in the context of pediatric dentistry.^{2, 3, 10} However, the significance of utilizing nitrous oxide and oxygen in conjunction with P.O. moderate sedation drug regimens is not often emphasized when analyzing drug regimens in pediatric dentistry.

While there are clear indications and advantages to nitrous oxide use, there are significant contraindications and disadvantages to nitrous oxide use as well.⁵¹ In dentistry, contraindications to nitrous oxide use include an inability to breathe through the nose, upper respiratory tract infections, chronic obstructive pulmonary disease, severe emotional disturbances or drug-related dependencies, first trimester of pregnancy, treatment with bleomycin sulfate, methylenetetrahydrofolate reductase deficiency, and “gas-filled space conditions” such as acute otitis media.^{50, 51} Disadvantages include lack of potency, dependency on psychological reassurance, interference of the nasal hood with injection to the maxillary anterior region, nitrous oxide pollution and potential occupational exposure health hazards, risk of nausea and vomiting, especially with fluctuations in concentrations and with extended use, and the potential for diffusion hypoxia if nitrous oxide administration is abruptly stopped without administration of appropriate amounts of oxygen.^{50, 51}

When used in pediatric dentistry, the most common adverse effect of nitrous oxide and oxygen inhalation sedation is nausea and vomiting, which occurs in approximately 0.5% of patients.^{50, 52} However, the contributions of nitrous oxide to the

overall incidence of adverse events when evaluating a moderate sedation drug regimen should not be overlooked. As Levering and Welie explain:

Additional risks are posed by the combination of N₂O with other sedative drugs given by a different route. Their actions become synergistic, and the potential for CNS depression is magnified, resulting in deeper sedation than desired or anticipated... with co-medications, reflexes may become compromised and patients risk aspiration in the event of vomiting, particularly if preoperative fasting was recommended but not observed. Such polypharmacy, including the combination of N₂O with local anesthetics that reach high serum levels, may even lead to respiratory arrest.⁵¹

Additional research is warranted in exploring the “additional risks” posed by combining nitrous oxide and oxygen inhalation sedation with P.O. drug regimens.

2.7 Aims, Hypothesis, and Significance

The aim of this study was to evaluate the safety and efficacy of a moderate sedation drug regimen consisting of P.O. morphine (0.66 mg/kg, up to a maximum of 30 mg), hydroxyzine (25 mg flat dose), and ibuprofen (100 mg flat dose), as utilized with nitrous oxide and oxygen sedation. We hypothesized that morphine might serve as a viable alternative opiate to meperidine for use in P.O. moderate sedation drug regimens in pediatric dentistry. With the current trend of restricting meperidine use or removing meperidine from hospital formularies altogether, many pediatric dentists may soon desire an opiate drug other than meperidine for use in their sedative drug regimens. Additionally, given the lack of data on morphine use in P.O. moderate sedation drug regimens in pediatric dentistry, we hope to stimulate further research on this topic.

3. METHODS AND MATERIALS

3.1 Methods and Materials Introduction

This study was approved by the Committee on Human Research at the University of California, San Francisco (IRB Number 10-03500). This was a retrospective study of a P.O. moderate sedation drug regimen (0.66 mg/kg morphine, 25 mg hydroxyzine, and 100 mg ibuprofen, as utilized with 50% nitrous oxide and 50% oxygen inhalation sedation), based on a convenience sample of sedation records obtained from a private group dental practice, Alameda Pediatric Dentistry / Pleasanton Pediatric Dentistry (APD/PPD).

3.2 Standard Operating Procedures of the Dental Practice Studied

Fundamental to the understanding of this study is an understanding of the standard operating procedures of the dentists at the private group dental practice APD/PPD.

All sedations performed by the dentists at APD/PPD followed a standardized sedation protocol when using the drug regimen of interest (0.66 mg/kg morphine, 25 mg hydroxyzine, 100 mg ibuprofen, and 50% nitrous oxide and 50% oxygen). After a discussion of the risks and benefits of different treatment modalities, patients thought to benefit from sedation because of behavioral and/or dental issues were selected from the private group practice APD/PPD. The patients were then scheduled to have comprehensive dental treatment performed by a dentist and aided by a P.O. moderate sedation drug regimen. This section will discuss the sedation protocols specifically pertaining to the drug regimen of interest.

Patients undergoing P.O. moderate sedation were instructed to follow NPO guidelines as outlined by the American Society of Anesthesiologists and endorsed by the American Academy of Pediatric Dentistry.⁵³ Upon arrival to the dental clinic on the day of the sedation appointment, medical and dental histories were reviewed, consent is obtained or confirmed, baseline vital signs were recorded (e.g. oxygen saturation, pulse, blood pressure), lungs were auscultated, and the airway was evaluated. The indications for sedation were recorded in the section of the sedation monitoring sheet entitled “SEDATION INDICATIONS”, and information regarding the airway was recorded in the section of the sedation monitoring sheet entitled “AIRWAY STATUS” (see Appendix 8.2).

Once the patient was deemed acceptable for sedation, the oral medications were administered (0.66 mg/kg morphine, 25 mg hydroxyzine, and 100 mg ibuprofen). This was achieved in a variety of ways. The clinician could give the patient a cup from which to drink the medications. Alternatively, the clinician could use a “needleless syringe” to “squirt” the medication into the patient’s mouth. If necessary, a mouth prop could be used to assist in keeping the patient’s mouth open during administration of the medications. The time that the oral medications were administered were recorded for each patient (“RX TIME” on the sedation log sheet; see Appendix 8.2). APD/PPD protocol after administration of the oral medications was to then wait approximately one hour before bringing the patient back to the dental operatory.

Sedated patients at APD/PPD were typically placed in protective stabilization when receiving dental treatment with oral conscious sedation, but some variation remained. Most often, protective stabilization included use of a Papoose Board (see

Appendix 8.2). Occasionally, however, only the “wrist straps” were used, and in rare instances no protective stabilization was used at all.

The time that the patient were brought into the dental operatory, placed in protective stabilization when appropriate, and/or began to have nitrous oxide and oxygen administered, was recorded on the sedation sheet on the row that states: “Set up Patient” in the notes (see Appendix 8.2). During the sedation appointment, vital signs (oxygen saturation, pulse, blood pressure) and behavior were recorded by dental auxillary staff at regular time intervals. In regards to recording behavior data, dental auxillary staff were trained and instructed to record the patient’s behavior according to “behavioral codes” as outlined by the dentists in the office, namely: SL=sleeping, Q=quiet, C=crying, and ST=struggling. Vital signs and behavioral codes were collected approximately every 5 minutes until the patient was allowed to leave the dental operatory and go to the recovery area.

As part of APD/PPD protocol, at approximately 5 p.m. on the day of the sedation appointment, a follow-up phone call was then placed by either the operating dentist or by one of the auxiliary staff. A series of standardized questions were then asked regarding the patient’s status post operatively, including napping behaviors, nausea/vomiting, and breathing problems. This data was then recorded on the sedation monitoring sheet (see Appendix 8.2) and kept with the physical dental chart.

3.3 Subjects and Study Design

A convenience sample of 595 sedation records (consisting of the electronic dental record, the sedation monitoring sheet, and/or the physical dental chart) were

chronologically screened from the dental records at the private group dental practice APD/PPD, dated from 8/7/2008 to 3/10/2011.

All data was physically entered into REDCap Database Software at a single location, the private practice dental office Alameda Pediatric Dentistry (2125 Whitehall Place, Alameda, CA 94501), and was password protected and stored on an encrypted network drive. The only identifier remaining after data entry was the dental chart number, known only to the dentists and staff at APD/PPD.

Inclusion criteria for the study were:

- 1) Patients were of record at the private group dental practice APD/PPD;
- 2) patients were ASA-1 or ASA-2;
- 3) upon pre-sedation evaluation, patients were determined to have extensive dental work and/or additional factors warranting moderate sedation;
- 4) patients were sedated with a drug regimen that closely approximates the drug regimen of interest: 0.66 mg/kg P.O. morphine, 25 mg flat dose P.O. hydroxyzine, 100 mg flat dose P.O. ibuprofen, and nitrous oxide and oxygen inhalation sedation;
- 5) records had adequate data for analysis;
- 6) patients were younger than 12 years old;
- 7) patients were 2 years of age or older.

Exclusion criteria for the study were:

- 1) Patients were of ASA-3 or greater; upon pre-sedation evaluation, patients were determined to have complicating medical issues and/or airway issues making patients unsuitable for sedation. This includes history of uncontrolled seizure disorder, history of cyanotic heart disease or other cyanotic cardiovascular condition, hypertrophic tonsils (“kissing tonsils”), or patients with airways deemed unsuitable for sedation;
- 2) patients were not sedated with drug regimen of interest;
- 3) records had inadequate data for analysis;
- 4) patients were 12 years of age or older;
- 5) patients were younger than 2 years old.

3.4 Data Collection and Data Entry

After inclusion and exclusion of patients as defined by the research protocol, selected sedation records were then analyzed for data of interest (table 1).

Table 1. Data of Interest

Chart Number	Amount of hydroxyzine given to patient (mg)	Dismissal time	Number of behavioral codes in each category
Date of service	Amount of ibuprofen given to patient (mg)	Lowest oxygen saturation recorded (%) w/o crying or struggling	Sedation indications
Age (years, months)	How well patients took oral medications	Highest systolic pulse w/o crying or struggling	Airway status
Gender (male/female)	Amount of 2% lidocaine w/ 1:100,000 epinephrine administered (mg)	Lowest pulse	Sedation indications

Weight (lbs; then translated into kg)	Amount of 4% septocaine w/ 1:100,000 epinephrine administered (mg)	Highest systolic blood pressure w/o crying or struggling	Airway status
Time of last meal	Time oral medications were given to patient	Highest diastolic blood pressure without crying or struggling	Behavioral data based on modified Frankl Scale
Name of operating dentist	Time of beginning of operative procedure	Lowest systolic blood pressure	Time of post-operative report
Amount of morphine given to patient (mg)	Time of end of operative procedure	Lowest diastolic blood pressure	Answers to post-operative questions

This “data of interest” was then entered into REDCap (Research Electronic Data Capture) database software, which was password protected and stored on an encrypted network drive. The REDCap database software could then export the data into Microsoft Excel and/or other data formats for further manipulation. Some of the above data of interest, entered for each record when available, warrant further clarification.

For example, for the majority of patients, the categories listed in the “SEDATION INDICATIONS” section of the sedation monitoring sheet (see Appendix 8.2) appeared to be adequate. These included “Age”, “Resistant”, “Hysterical”, “Combative”, “Physical disability”, “Extensive treatment”, “Excess activity”, “Learning disability”, “Mental disability”, and “Immature development”. However, in a small number of the sedation monitoring sheets, additional categories were handwritten in the “SEDATION INDICATIONS” section, including “Anxious” and “Gagger”. These handwritten categories were not tabulated or included in the final analysis of behavioral data. Conversely, in many of the sedation records, the dentist or dental auxiliary staff indicated more than one indication for sedation. In recording this data, every category that was marked was tabulated and included in final analysis. For example, if a patient

was both young and had extensive dental needs, both “Age” and “Extensive treatment” would be marked in the “SEDATION INDICATIONS” section of the sedation monitoring sheet.

Airway status data was additionally collected (see the “AIRWAY STATUS” section in Appendix 8.2). However, after collection of this data, an uncharacteristic lack of standardization prompted the authors of this study to disregard the data. Accordingly, this data was not included in final data analysis.

Similar to records of “Sedation indications”, the sedation monitoring sheet contained a number of defined descriptors for how well the patient took the oral medications. These include: “Well”, “Syringe”, “Struggled”, “Cried”, “Spit out”, and “Mouth-prop”. If the patient exhibited more than one behavior during administration of the oral medications, the dentist or dental auxiliary staff would sometimes mark more than one descriptor. For example, if a patient struggled, cried, and had medications administered through a “needleless syringe”, the dentist or dental auxiliary staff would make “Struggled”, “Cried”, and “Syringe” on the sedation monitoring sheet.

In regards to “Time of beginning of operative procedure”, the time was entered when 50% nitrous oxide and 50% oxygen was administered to the patient, as the dental operative procedure typically began at that time point or shortly thereafter. This typically corresponds to the “Set up Patient” row as explained in Section 3.1. In regards to “Time of end of dental operative procedure”, the time was entered when 50% nitrous oxide 50% oxygen was turned off, or when the dental assistant otherwise indicated in the “notes” section of the record that the dental procedures were completed. “Dismissal time” was the time that the patient was dismissed from the dental clinic and allowed to

go home after completion of the dental procedure and appropriate recovery from the sedation. “Time of post-operative report” was the time that the dentist or auxiliary staff called the patient to ask post-operative questions (e.g. “Was your child able to eat and/or drink?”)

Once each of these time points (“Time of beginning of operative procedure”, “Time of end of operative procedure”, and “Dismissal Time”, as well as “Time oral medications were given to patient”) were determined, time interval data was then extrapolated. “Wait time”, defined as the time period spanning from the administration of the oral medications to the beginning of dental operative procedures, was determined by subtracting “Time oral medications were given to patient” from “Time of beginning of operative procedure”. Likewise, “Working Time” was determined by subtracting “Time of beginning of operative procedure” from “Time of end of operative procedure”. “Recovery Time”, defined as the amount of time spanning from the completion of the dental operative procedure until the patient is deemed safe for discharge from the dental clinic, was similarly be determined by subtracting “Time of end of operative procedure” from “Dismissal Time”.

One way to approximately quantify the extent of dental treatment received by pediatric dental patients is to quantify the number of “sextants” worked on by the operating dentist. In this classification scheme, teeth are categorized by the following sextants: upper right (teeth #A-B, or #1-5), upper anterior (teeth #C-H, or #6-11), upper left (teeth #I-J, or #12-16), lower left (teeth #K-L, or #17-21), lower anterior (teeth #M-R, #22-27), and lower right (teeth #28-32). Not only does this classification scheme provide an estimate of the number of teeth worked on during the sedation appointment,

but it also is informative in regards to the number of anatomical sites requiring local anesthetic administration. Accordingly, for each patient receiving dental treatment by the dentists at the private group practice APD/PPD, the number of sextants of dentistry performed during the sedation appointment was quantified when possible (1-6).

Cardiovascular data was analyzed in an effort to exclude data reflecting alterations due to patient behavior such as crying and/or struggling (e.g. exclusion of oxygen desaturations due to crying and/or struggling rather than “true” oxygen desaturations due to loss of muscle tone and/or decreased respiratory drive). Accordingly, oxygen saturation recordings were only included as “lowest oxygen saturation recorded (%)” if the patient was not crying and/or struggling, or exhibiting other behavioral codes indicative of an awake but misbehaving child. In doing so, it was assumed that most oxygen desaturations due to prolonged crying, intentional breath holding, and /or struggling were eliminated, and that desaturation events displayed in the “Lowest Oxygen Saturation” section reflect “true” oxygen desaturations and can be considered an adverse event. Likewise, high pulse and high blood pressure readings were only included if the patient was not crying and/or struggling. The goal of doing this was to eliminate high pulse and blood pressure readings that were due to increased exertion related to uncooperative behavior. Lowest pulse and lowest blood pressure readings were included regardless of behavioral code.

After initial analysis of cardiovascular data and indicators of adverse events, all records identified as having data suggestive of hypotension, tachycardia, bradycardia, or adverse events were re-retrieved and further analyzed for overall cardiovascular stability. For the purposes of this study, hypotension in pediatric patients was defined as patients

with a systolic blood pressure less than the fifth percentile by age, as outlined by recognized standards.⁵⁴ Parameters for tachycardia and bradycardia in the pediatric population were less clearly defined in the literature. For the purposes of this study, tachycardia in the pediatric population was defined as a pulse of greater than the 99th percentile by age, and bradycardia in the pediatric population was defined as a pulse of less than the 1st percentile by age.⁵⁵

The recording of “behavioral codes” warrants further clarification. As aforementioned, the standard operating procedures at the group dental practice APD/PPD calls for dental auxiliary staff to record the behavior of patients undergoing sedation at each time interval recorded. The standardized “behavioral codes” were: SL=sleeping, Q=quiet, C=crying, and ST=struggling. Alternatively, however, the dental auxiliary staff could write down their behavior using whatever language desired. For the purposes of this study, these hand written behavior codes were lumped into the O=other category, and represent a wide range of entries, including “happy”, “talking”, good”, “calm”, “OK”, and “mumbling”. At some of the time intervals, numerous behavior codes were utilized. In this case, the more extreme behavioral code was recorded. For example, if Q=quiet and SL=sleeping were both listed, SL=sleeping would be listed. Conversely, if C=crying and ST=struggling were both listed, ST=struggling would be listed.

3.5 Data Analysis

The 360 selected records were analyzed for each of the variables listed in Figure 2. For quantitative data based on an interval scale, descriptive statistics such as mean,

standard deviation, standard error of the mean, minimum value, median, and maximum value were calculated as appropriate. For qualitative or categorical data based on a nominal scale, quantification of this data was accomplished through tabulating the number of patients in each defined group, and percentages were calculated.

4. RESULTS

4.1 Patient Selection and Demographics

From the initial convenience sample of 595 records, 170 records were excluded due to the patients not being sedated with the drug regimen of choice. These records contained data pertaining to sedation regimens consisting of morphine + hydroxyzine (150 records), morphine + hydroxyzine + acetaminophen (1 record), “other” morphine regimens or “morphine” regimens with unspecified dosages (6 records), midazolam (11 records), midazolam + hydroxyzine (1 record), and midazolam + ibuprofen (1 record).

Of the remaining 425 records, an additional 52 were excluded because the records had inadequate data for analysis. More specifically, 45 sedation records were missing the sedation log sheets and/or the dental chart, 5 sedation records had data that was determined to be unusable, and 2 sedation records were unusable due to the sedation appointment being cancelled due to patient behavior.

Of the remaining 373 sedation records, an additional 13 were excluded because they fell outside of the age criteria. More specifically, 3 patient records were excluded because the patients were under 2 years of age, and 10 patient records were excluded because they were older than 12 years of age. Patients that were sedated that were older than 12 years of age were typically autistic or special needs patients, or required

extensive dental treatment that was surgical in nature. After exclusion of these records, the final sample size was 360 (Figure 1).

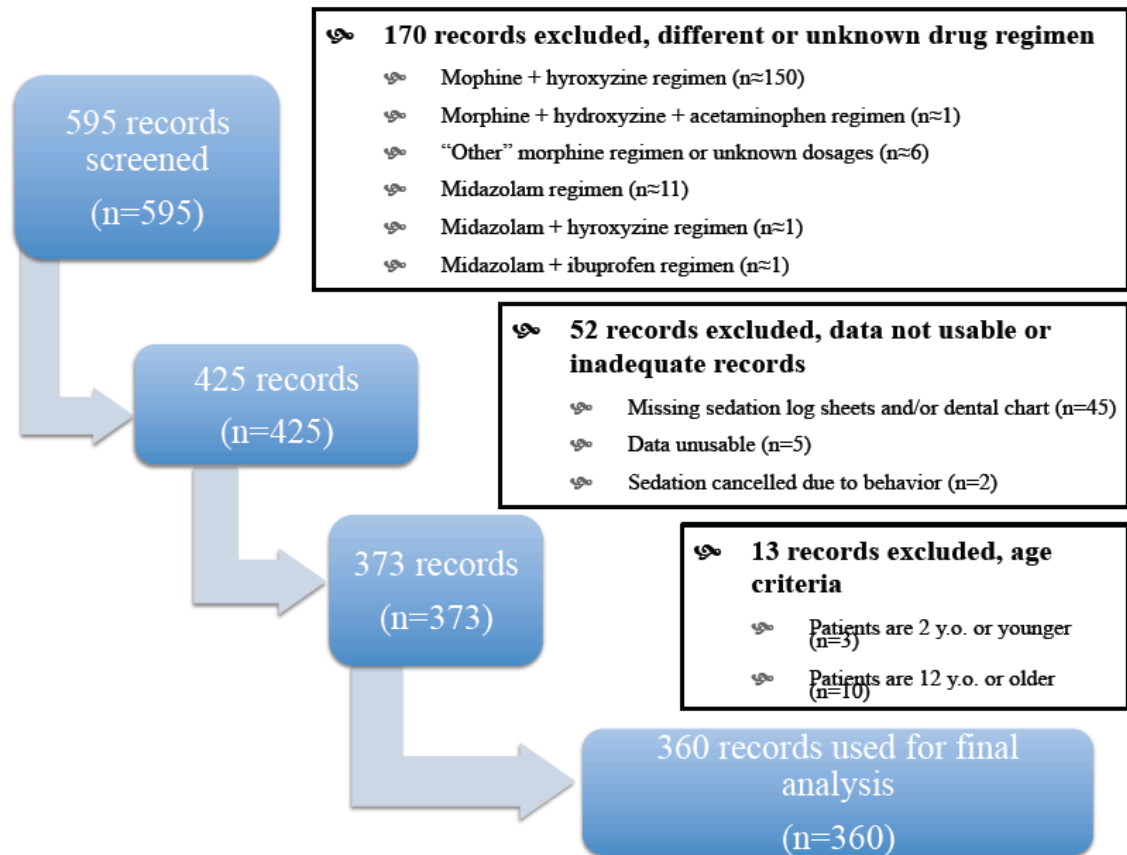


Figure 1: **Flow chart of patient selection**

Patients had a mean age of 5.25 years, with a standard deviation (SD) of 1.76 years, and a standard error of the mean of 0.09 years (n=360). The median age was 4.96 years. The minimum age included in the study, as defined by the inclusion and exclusion criteria was 2 years, and the maximum age was 11.83 years. The age distribution did not follow a normal distribution, but rather, had a “bulk” of patients in the 3-year-old to 6-year-old age range (Figure 2).

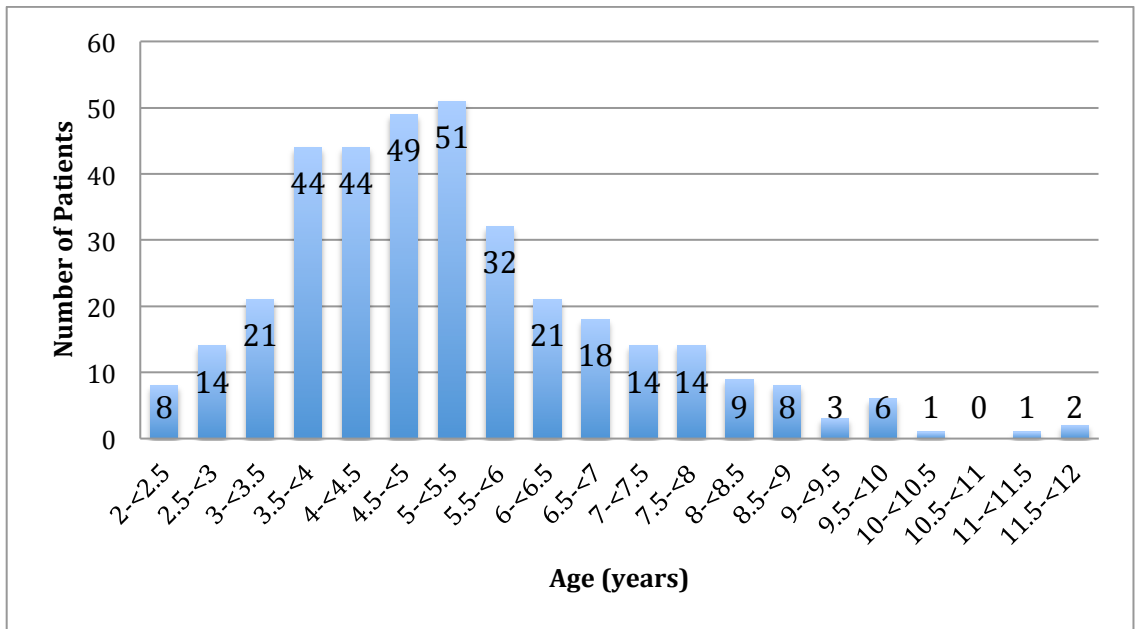


Figure 2: **Patient ages in years**

Patients had a mean weight of 19.96 kg, with a standard deviation of 5.55 kg and a standard error of the mean of 0.29 kg (n=360). The median weight was 18.64 kg. The minimum weight was 9.55 kg, and the maximum weight was 43.18 kg. The weight distribution similarly did not follow a normal distribution, and a “bulk” of patients fell into the 15 kg to 25 kg weight range (Figure 3).

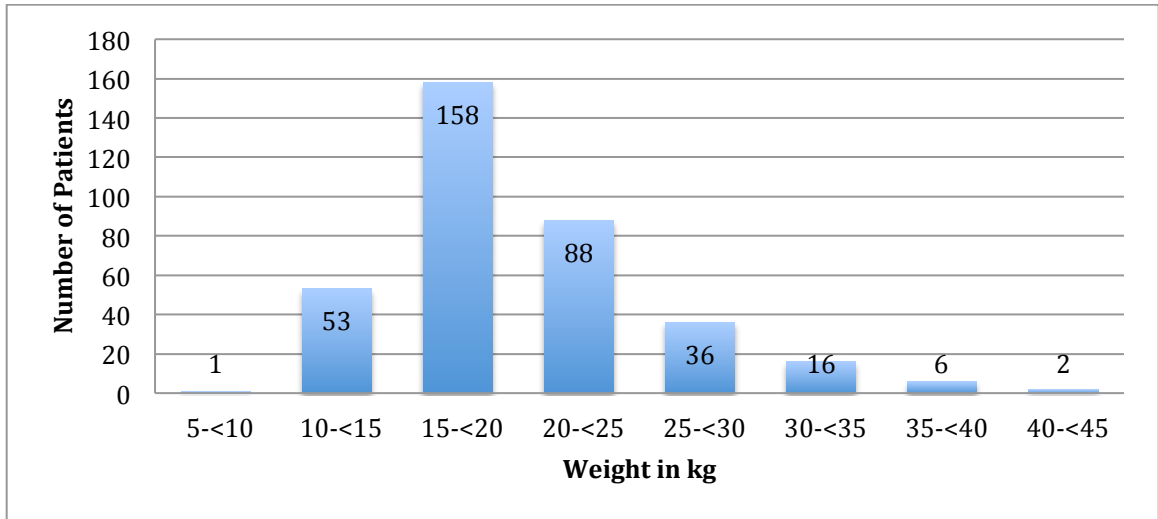


Figure 3: Patient's weight in kg

The distribution of males and female was roughly equal, with 178 males (49.4%) and 182 females (50.6%) being included in the study (n=360) (Figure 4).

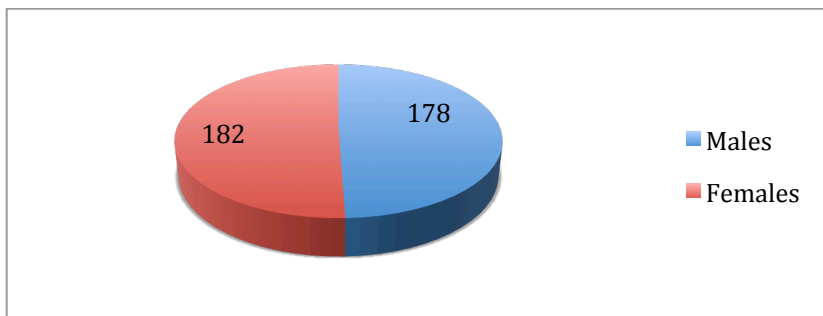


Figure 4: Distribution of gender (male/female) in patients

As aforementioned in section 3.4, and observed in Appendix 8.2, recognized criteria for sedation indications listed on the sedation monitoring sheet included “Age”, “Resistant”, “Hysterical”, “Combative”, “Physical disability”, “Extensive treatment”,

“Excess activity”, “Learning disability”, “Mental disability”, and “Immature development”. 278 of the 360 records included for final analysis listed indications for sedation; the remainder of the sedation records left the “SEDATION INDICATIONS” section of the sedation monitoring sheet blank. Of those, many records listed more than one indication for sedation. The most common indications for sedation, often found in combination with each other, were “Age” (222 out of 278 sedation records, or 79.9%) and “Extensive Treatment” (209 out of 278 sedation records, or 75.2%). Although collected separately, in final analysis the categories of “Resistant”, “Hysterical”, and “Combative” were combined due to similarity, and were subsequently treated as one category. This category, “Resistant/Hysterical/Combative” constitutes the third most common reason for sedation (90 out of 278 sedation records, or 32.4%). The full results for sedation indications can be found in Table 2.

Table 2.

Sedation Indications (n=278)

	Yes	% Yes
Age	222	79.9%
Extensive Treatment	209	75.2%
Resistant/Hysterical/Combative	90	32.4%
Excess Activity	13	4.7%
Mental Disability	6	2.2%
Immature Development	1	0.4%
Learning Disability	1	0.4%
Mental Disability	1	0.4%

4.2 Medications Administered

This study is interested in the P.O. moderate sedation drug regimen of interest, namely 0.66 mg/kg morphine, 25 mg hydroxyzine (flat dose), and 100 mg ibuprofen (flat dose), as utilized with 50% nitrous oxide 50% oxygen. However, the amount of P.O. morphine administered, although tightly regulated and standardized, sometimes varied slightly from the intended 0.66 mg/kg. More specifically, the amount of P.O. morphine administered to patients had a mean of 0.651 mg /kg weight, with a standard deviation of 0.0559 mg/kg and a standard error of the mean of 0.00295 mg/kg (n=360). The median amount of P.O. morphine administered was 0.66 mg/kg. The minimum amount of P.O. morphine administered was 0.27 mg/kg, and the maximum was 1.16 mg/kg. The distribution of P.O. morphine administered to patients, as well as related descriptive statistics, is shown in Figure 5.

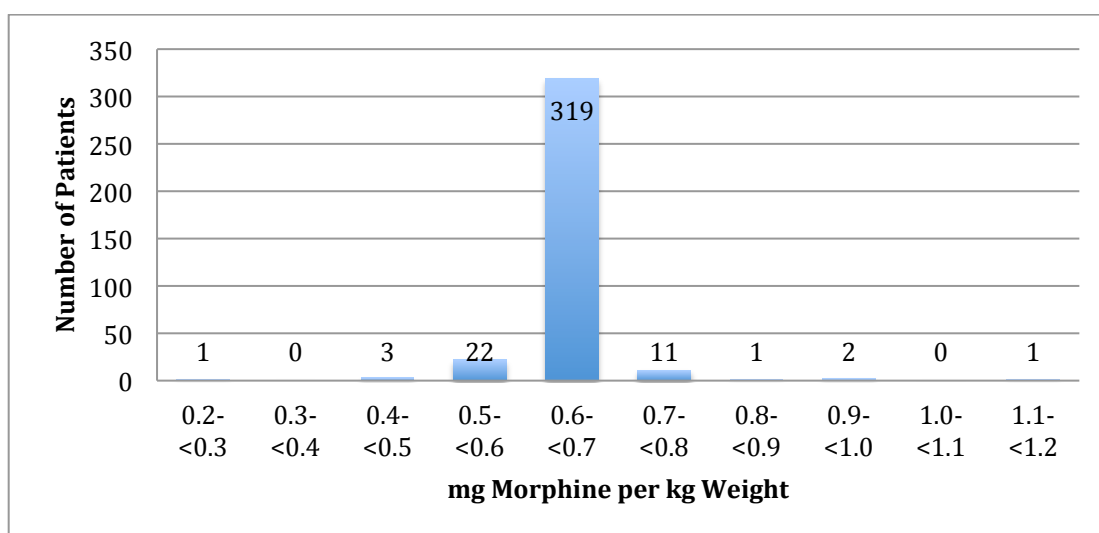


Figure 5: Mg of morphine per kg weight

The amount of P.O. hydroxyzine administered to all patients (n=360) was exactly 25 mg, and the amount of P.O. ibuprofen administered to all patients (n=360) was exactly 100 mg. Because the weight of the patients varied, however, the mg P.O. hydroxyzine administered to patients per kg weight, as well as the mg P.O. ibuprofen administered to patients per kg weight, varied among patients.

The amount of P.O. hydroxyzine administered to patients had a mean of 1.335 mg/kg, with a standard deviation of 0.3318 mg/kg and a standard error of the mean of 0.01749 mg/kg (n=360). The median amount of P.O. hydroxyzine administered was 1.341 mg/kg. The minimum amount of P.O. hydroxyzine administered was 0.309 mg/kg, and the maximum was 2.619 mg/kg. The distribution of P.O. hydroxyzine administered to patients, as well as related descriptive statistics, is shown in Figure 6.

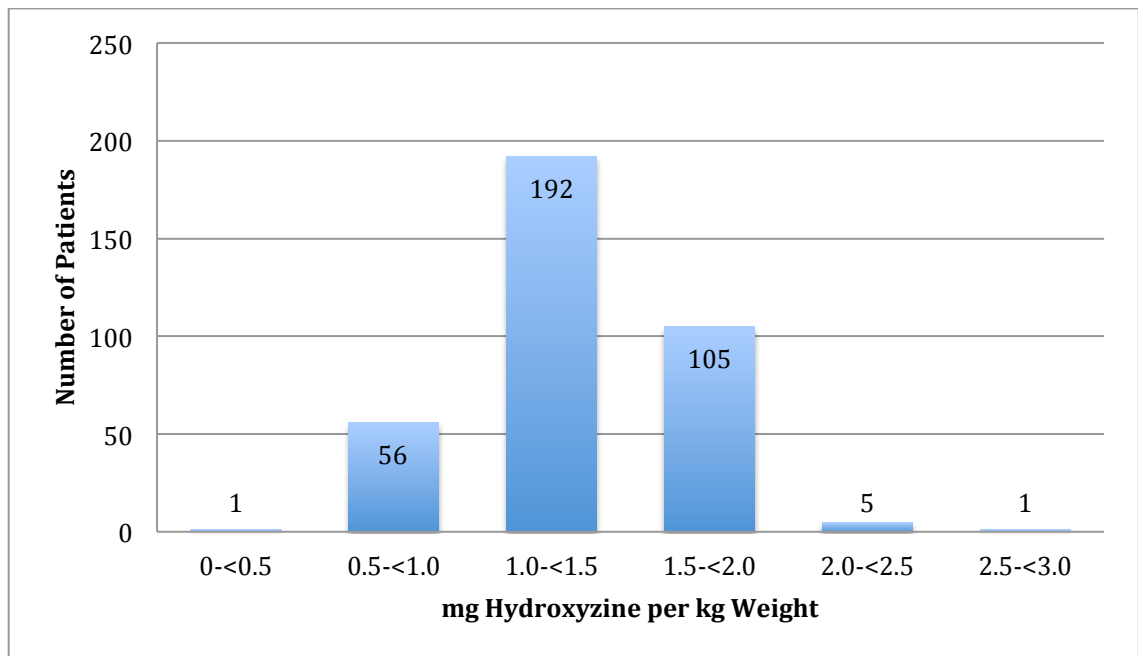


Figure 6: Mg of hydroxyzine per kg weight

The amount of P.O. ibuprofen administered to patients had a mean of 5.351 mg/kg, with a standard deviation of 1.3097 mg/kg and a standard error of the mean of 0.0690 mg/kg (n=360). The median amount of P.O. ibuprofen administered was 5.366 mg/kg. The minimum amount of P.O. ibuprofen administered was 2.316 mg/kg, and the maximum was 10.476 mg/kg. The distribution of P.O. hydroxyzine administered to patients, as well as related descriptive statistics, is shown in Figure 7.

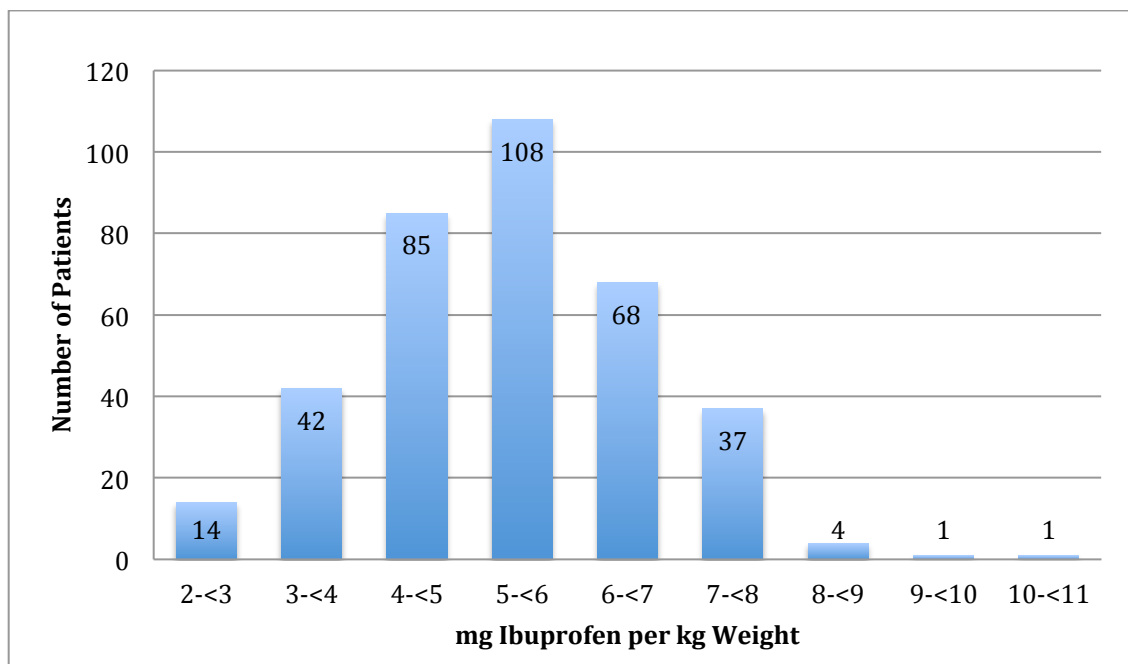


Figure 7: Mg ibuprofen per kg weight

4.3 Ease of Administration of Oral Medications

342 out of 360 sedation records (95%) included data on how well oral medications were taken by the patient. Of these, 309 out of 342 sedation records (90.4%) reported that patients took the oral medications “Well”. Conversely, 29 out of 342

sedation records (8.5%) reported that patients “Cried”. 28 out of 342 sedation records (8.2%) reported that a needleless syringe was used (“Syringe”). 24 out of 342 sedation records (7.0%) reported that patients “Struggled”. 16 out of 342 sedation records (4.7%) reported that a mouth-prop was used (“Mouth-prop”). 9 out of 342 sedation records (2.6%) reported that the patients spit out either some or all of the oral medication (“Spit out”). If more than one descriptive category fit the behavior of the child during administration of the oral medications, then both items were marked. Most commonly, patients who exhibited uncooperative behavior such as crying exhibited additional behaviors such as struggling, or necessitated the use of a mouth-prop. Full results for how well patients took oral medications can be seen in Figure 3.

Table 3. How Well Patients Took Oral Medications

	Yes	% Yes
Well	309	90.4%
Cried	29	8.5%
Syringe	28	8.2%
Struggled	24	7.0%
Mouth-prop	16	4.7%
Spit out	9	2.6%

4.4 Wait Time

As discussed in Section 3.2, the protocol of the dentists in the private group practice APD/PPD was to wait approximately 60 minutes after administration of the oral medications before bringing patients back to the dental operatory and placing them in

protective stabilization, when appropriate. However, in daily practice, some variation persisted in regards to this “wait time”. More specifically, the mean wait time was 64.66 minutes, with a standard deviation of 16.84 minutes, and a standard deviation of the mean of 0.90 minutes (n=351). The median wait time was 63 minutes. The minimum “wait time” was 0 minutes, and the maximum wait time was 145 minutes. A more detailed description of wait time experienced by patients can be found in Figure 8.

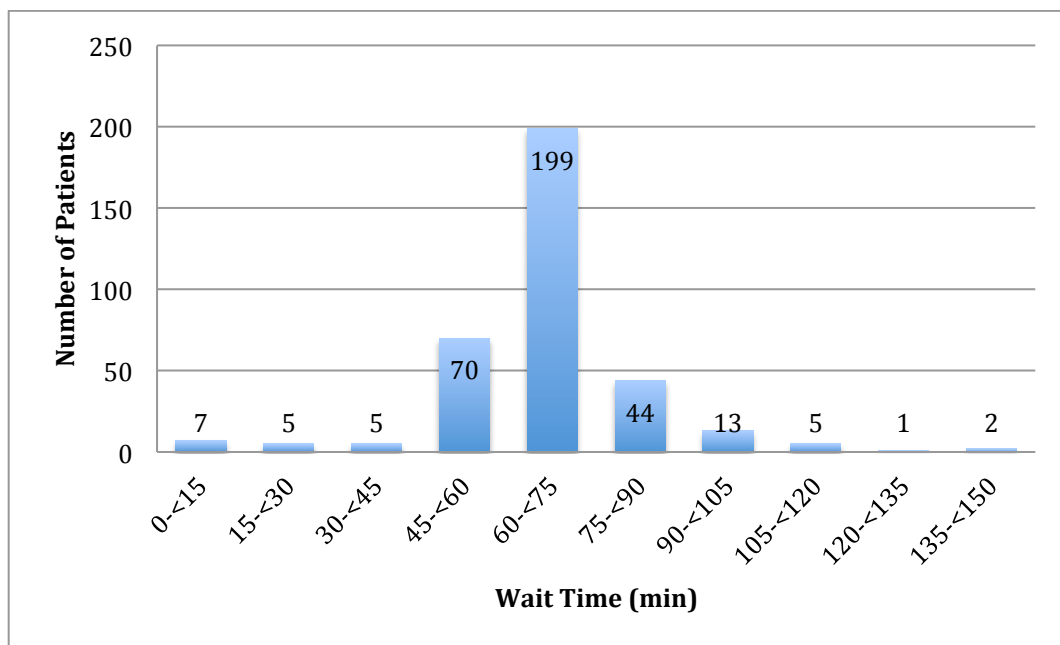


Figure 8: Wait time (min)

4.5 Local Anesthetic(s) Administered

2% lidocaine with 1:100,000 epinephrine was the primary local anesthetic agent utilized by the dentists in the private group dental practice APD/PPD. The mean amount (in mg) of lidocaine administered per kg bodyweight, always in solution as 2% lidocaine with 1:100,000 epinephrine, was 4.31 mg/kg (n=355). The standard deviation was 1.70

mg/kg, and the standard error of the mean was 0.09 mg/kg. The median amount of lidocaine (mg) administered per kg bodyweight, was 4.19 mg/kg. The minimum amount of lidocaine (mg) administered per kg bodyweight was 0.41 mg/kg, and the maximum was 12.98 mg/kg. It should be noted that an analysis of lidocaine administration revealed that 149/355 sedation records, or 42.0%, had lidocaine dosages exceeding the American Academy of Pediatric Dentistry (AAPD) maximum recommended dosage of 4.4 mg/kg.⁵⁶ Similarly, further analysis of lidocaine administration revealed that 16/355 sedation records, or 4.5%, had lidocaine dosages exceeding the more widely recognized maximum recommended dosage of 7.0 mg/kg.⁵⁷⁻⁵⁹ The distribution of lidocaine administration to patients is shown in Figure 9.

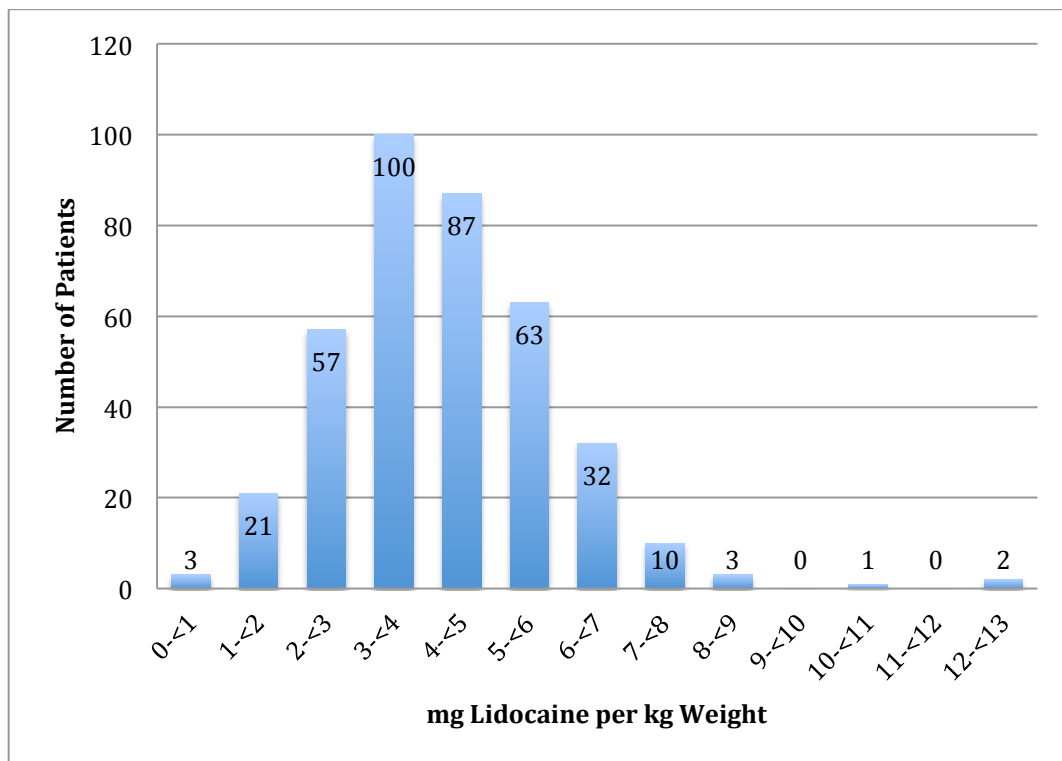


Figure 9: Mg of lidocaine per kg weight

In the majority of patients (338/355, or 95.2%), 2% lidocaine with 1:100,000 epinephrine was the sole local anesthetic agent. However, in a small number of patients (17/355, or 4.8%), 4% septocaine with 1:100,000 epinephrine was utilized to supplement local anesthesia. The mean amount (in mg) of septocaine administered per kg bodyweight, always in solution with 1:100,000 epinephrine, was 0.12 mg/kg (n=355). The standard deviation was 0.60 mg/kg, and the standard error of the mean was 0.03 mg/kg. The median amount of septocaine (mg) administered per kg bodyweight, was 0 mg/kg. The minimum amount of septocaine (mg) administered per kg bodyweight was 0 mg/kg, and the maximum was 5.11 mg/kg. The distribution of septocaine administration to patients is shown in Figure 10.

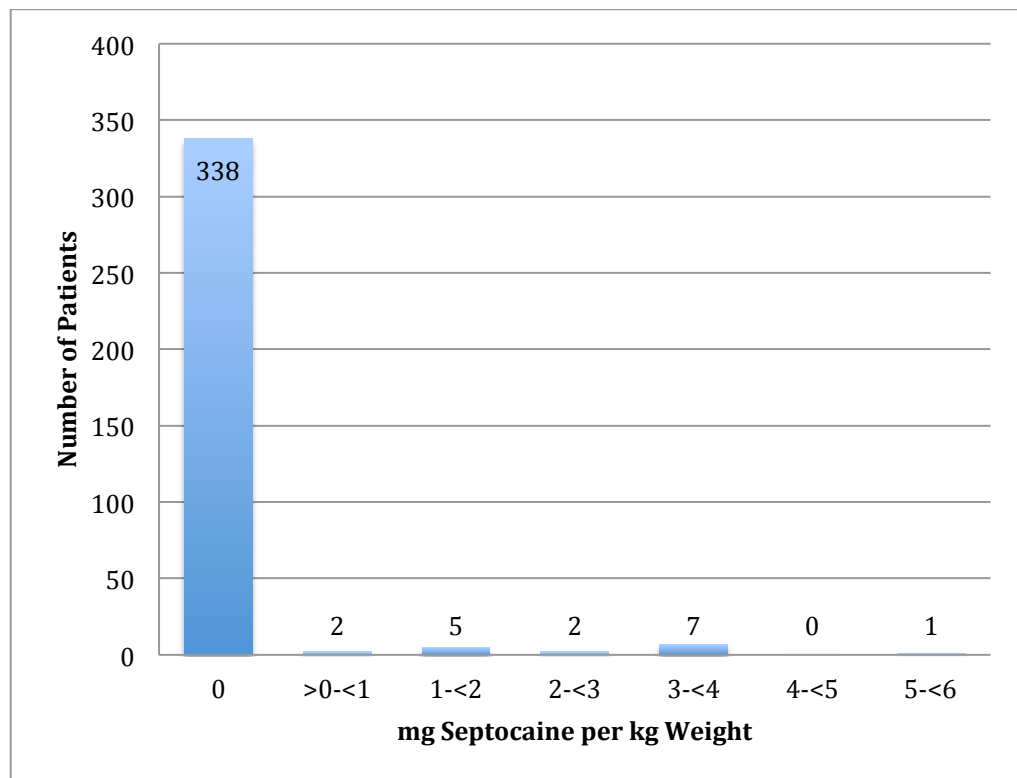


Figure 10: Mg of septocaine per kg weight

4.6 Number of Sextants of Dentistry Completed Per Sedation Appointment

The mean number of sextants of dentistry completed by the dentists at the group practice APD/PPD per sedation appointment was 3.82, with a standard deviation of 1.33 sextants, and a standard error of the mean of 0.07 sextants (n=350). The median number of sextants of dentistry completed per sedation appointment was 4. The minimum number of sextants of dentistry completed per sedation appointment was 1, and the maximum was 6. The distribution of the number of sextants of dentistry completed per sedation appointment can be found in Figure 11.

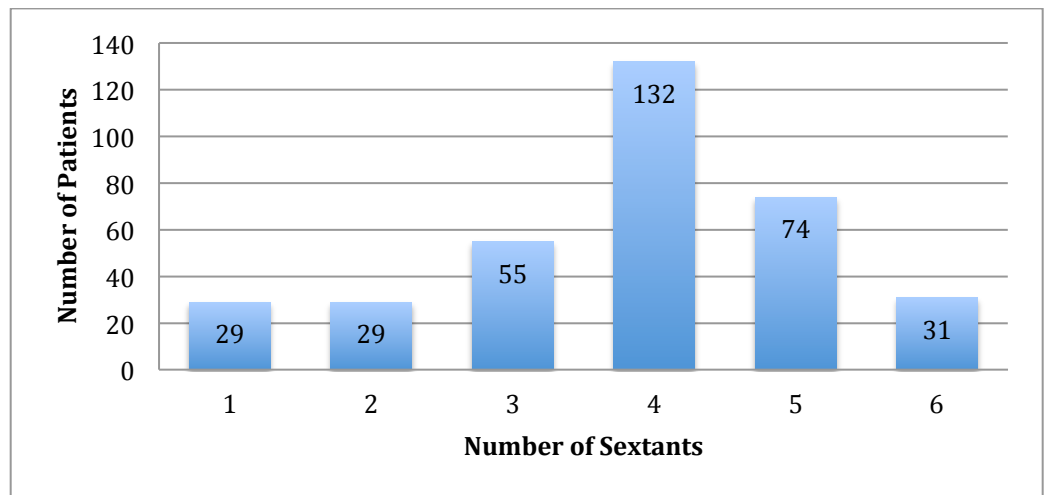


Figure 11: Number of sextants of dentistry completed per sedation appointment

4.7 Working Time

A commonly cited concept in sedation in pediatric dentistry is the concept of “working time”. This “working time” is an approximation of amount of time that

patients remain sedated after administration of a specific sedation drug regimen. As explained in section 3.4, working time could be estimated in this study by subtracting the objectively entered “Time of beginning of operative procedure” from the objectively entered “Time of end of operative procedure”. From this extrapolated data, the mean working time was 71.57 minutes, with a standard deviation of 26.81 minutes, and a standard error of the mean of 1.47 minutes. The median working time was 70 minutes. The minimum working time was 13 minutes, and the maximum working time was 195 minutes. The distribution of working time, during which dental operative procedures were performed by the dentists in the private group practice APD/PPD, can be seen in Figure 12.

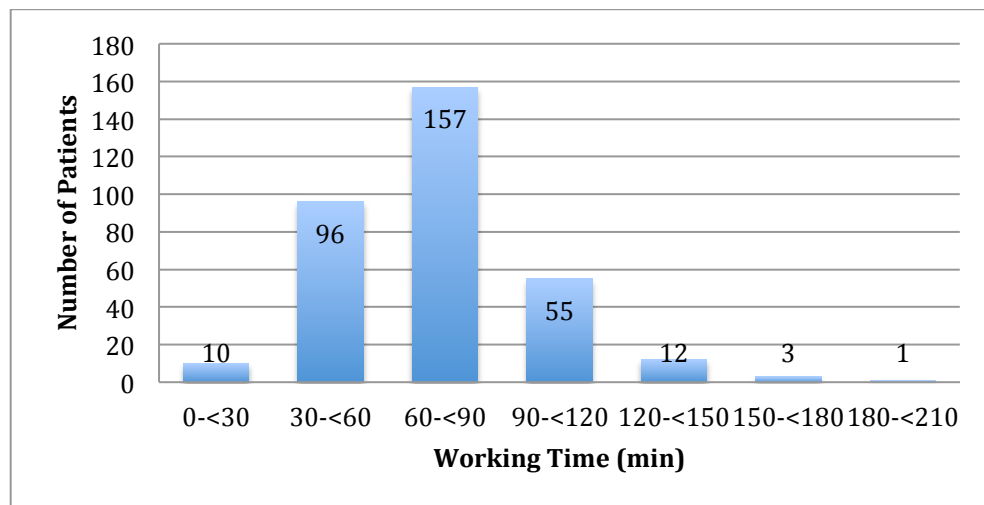


Figure 12: Working time (min)

4.8 Vital Signs and Physiologic Parameters

As outlined in section 3.4, each sedation record was evaluated for the lowest reading for oxygen saturation, as determined by pulse oximeter, when patients were not

crying or struggling. The mean lowest oxygen saturation reading for these records was 98.71, with a standard deviation of 1.14, and a standard error of the mean of 0.06 (n=330). The median lowest oxygen saturation reading for these records was 99. The minimum lowest oxygen saturation reading for these records was 87, and the maximum was 100. Data on the lowest oxygen saturation readings was not included for 30 of the 360 (8.3%) of sedation records included for final analysis. This was because the data was either missing, or because the patients were crying and/or struggling for the entire dental procedure. It should additionally be noted that 329 of the 330 records (99.7%) for which oxygen saturation data was available had lowest oxygen saturations of greater than 90; hence, true oxygen saturation only occurred in only one out of 330 records (0.3%). The distribution of lowest oxygen saturation readings can be found in Figure 13.

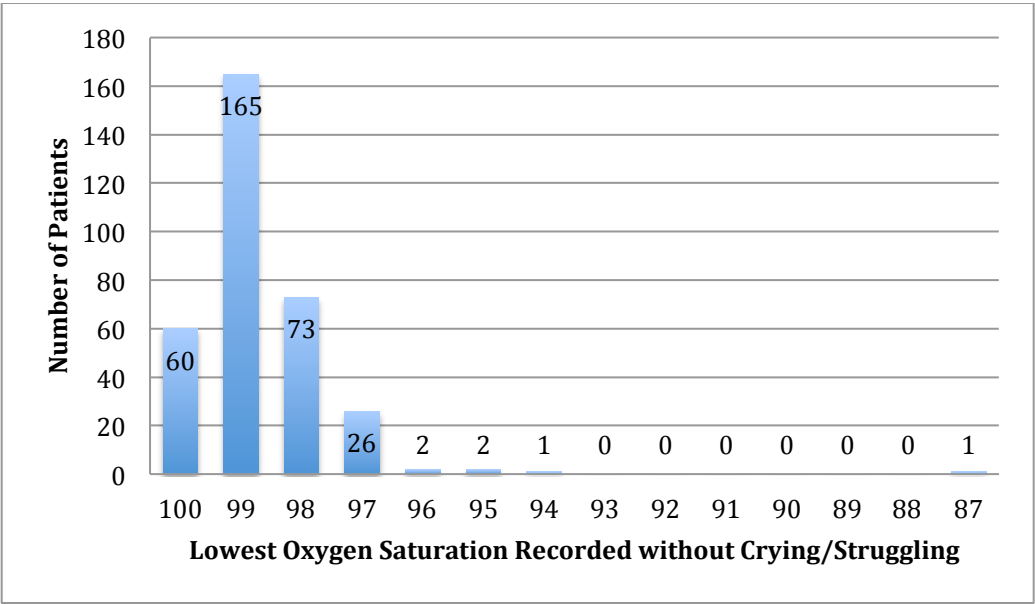


Figure 13: Lowest oxygen saturation recorded without crying/struggling

For each of the major cardiovascular parameters listed in Figure 1, the mean, the standard deviation, the standard error of the mean, the minimum value, the median value, and the maximum value were calculated. The results of this analysis can be found in Table 4.

Table 4. Cardiovascular Data

	Mean	SD	SEM	Min	Median	Max	N
Highest Pulse w/o Crying and/or Struggling	103.84	16.62	0.92	59	101	188	327
Lowest Pulse	85.78	16.00	0.86	19	84	164	349
Highest Systolic Blood Pressure w/o Crying or Struggling	122.36	15.79	0.89	46	122	166	317
Lowest Systolic Blood Pressure	103.90	15.56	0.84	55	104	157	341
Highest Diastolic Blood Pressure w/o Crying or Struggling	67.99	14.30	0.80	32	66	119	317
Lowest Diastolic Blood Pressure	51.45	10.61	0.57	20	51	95	342

As discussed in section 3.4, hypotension is defined in this study as having a systolic blood pressure of less than the fifth percentile by age.⁵⁴ Accordingly, for children age 1 to age 10, hypotension is defined as having a systolic blood pressure less than $70 \text{ mm Hg} + (2 \times \text{age in years})$; for children age 10 and older, hypotension is defined as having a systolic blood pressure of less than 90 mm Hg.⁵⁴

After re-retrieving and thoroughly analyzing all sedation records where hypotension was observed, the authors of this study found that each of these instances occurred in patients that were otherwise asymptomatic, and were stable overall in regards to cardiovascular parameters. For this reason, we have referred to these instances as “asymptomatic systolic hypotension”. The overall incidence of asymptomatic systolic hypotension was 18 out of the 340 sedation records (5.29%) where data was available. The breakdown of the instances of asymptomatic systolic hypotension by age can be found in Table 5.

Table 5. Asymptomatic Systolic Hypotension

	Number of Hypotensive Patients	Total Number in Category (n)	Percentage
Age 2	0	18	0%
Age 3	3	59	5.08%
Age 4	5	90	5.56%
Age 5	6	80	7.50%
Age 6	2	37	5.41%
Age 7	1	28	3.57%
Age 8	0	16	0%
Age 9	0	8	0%
Age ≥ 10	1	4	25.00%
TOTAL	18	340	5.29%

We defined tachycardia and bradycardia as having a pulse of greater than the 99th percentile by age and less than the 1st percentile by age, respectively (see Table 6).⁵⁵

Table 6. Definitions of Tachycardia and Bradycarida Utilized for this Study

	Tachycardia (Pulse > 99 th Percentile by Age)	Bradycarida (Pulse <1 st Percentile by Age)
Age 2	>142 bpm	<76 bpm
Age 3	>136 bpm	<70 bpm
Age 4 to Age 6	>131 bpm	<65 bpm
Age 6 to Age 8	>123 bpm	<59 bpm
Age 8 to Age 12	>115 bpm	<52 bpm

A review of the sedation records showed that in children with recorded instances of tachycardia and bradycardia, there was no associated signs of cardiovascular collapse, and patient data suggested an otherwise asymptomatic patient. Accordingly, we referred to these instances as “asymptomatic tachycardia” and “asymptomatic bradycardia”, respectively.

The overall incidence of asymptomatic tachycardia was 20 out of 327 sedation records (6.12%), and the overall incidence of asymptomatic bradycardia was 15 out of 349 sedation records (4.30%). The breakdown of the instances of asymptomatic tachycardia by age, and asymptomatic bradycardia by age, can be found in Table 7 and Table 8, respectively.

Table 7. Asymptomatic Tachycarida

	Number of Tachycardic Patients	Total Number in Category (n)	Percentage
Age 2	0	17	0%
Age 3	5	58	8.62%
Age 4 to Age 6	9	162	5.56%
Age 6 to Age 8	3	64	4.69%
Age 8 to Age 12	3	26	11.54%
TOTAL	20	327	6.12%

Table 8.

Asymptomatic Bradycardia

	Number of Bradycardic Patients	Total Number in Category (n)	Percentage
Age 2	3	20	15%
Age 3	1	63	1.59%
Age 4 to Age 6	9	173	5.20%
Age 6 to Age 8	2	65	3.08%
Age 8 to Age 12	0	28	0%
TOTAL	15	349	4.30%

4.9 Behavioral Data

Patient behavior was collected at each time interval provided for each sedation record, providing a total count of 3445 “behavioral codes” (SL=sleeping, Q=quiet, C=crying, and ST=struggling, or O=other) from a total of the 354 sedation records for which behavioral data was available. An analysis of these behavioral codes reveals that 2483 of the 3445 behavioral codes recorded, or 72.08%, were Q=quiet. 461 out of 3445 behavioral codes, or 13.38%, were C=crying. 208 out of 3445, or 6.08%, were ST=struggling. 157 out of 3445, or 4.56%, were O=other, and 136 out of 3445, or 3.95%, were SL=sleeping. Table 9 shows a table of this data, and Figure 14 illustrates this data as percentages of time spent in each in each behavioral category.

Table 9. Behavioral Data

Behavioral Code	Number of Behavioral Recorded (N=3445)	% of Behavioral Recorded	Total Codes
“Quiet”	2483	72.08%	
“Crying”	461	13.38%	
“Struggling”	208	6.04%	
“Other”	157	4.56%	
“Sleeping”	136	3.95%	

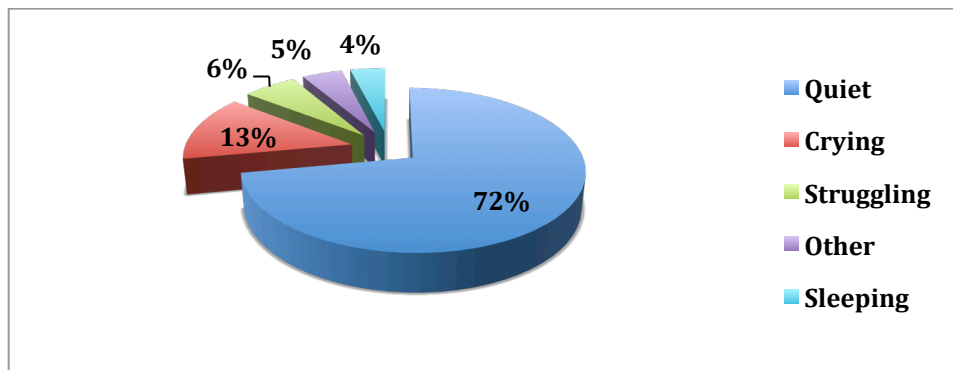


Figure 14: Behavioral data (2)

4.10 Significant Adverse Events

Of the 360 sedation records included in final analysis, five sedation records contained data indicative of a significant adverse event. This represents 1.4% of all sedation records included for final analysis.

One of the adverse events can be attributed to an incidence of a true oxygen desaturation. The sedation record in this one case (Figure 22) was of a 2 year, 2 month

old female patient who received three sextants of dental treatment and had a working time of 60 minutes. Notably, the patient had 98 mg of lidocaine administered (in solution as 2% lidocaine with 1:100,000 epinephrine) and weighed 11.82 kg, which equates to 8.29 mg/kg, well over the recommended dose of 4.4 mg/kg.⁶⁰ Over the course of this sedation, the oxygen saturation dropped to 95 at 10:25 a.m., then dropped to 87 at 10:30 a.m. At this point (10:30 a.m.), the nitrous oxide was turned off and the patient had 100% oxygen administered via a nitrous oxide mask. The operating dentist, however, continued work on the dental restorations. Oxygen saturation continued to read 87 at 10:35 a.m., but returned to 99 at 10:40 a.m. Based on data included in the sedation record, the remainder of the sedation visit was otherwise unremarkable. It should be noted, however, that the operating dentist noted that the tonsils were unable to visualize pre-operatively, and accordingly were not observed prior to sedation.

Three adverse events can be attributed to varying degrees of excessive sedation and/or prolonged sedation. In one of these sedation records, a 3 year 9 month female patient received five sextants of dental treatment, with the operating dentist completing this treatment in 95 minutes. The patient had 126 mg of lidocaine administered (in solution as 2% lidocaine with 1:100,000 epinephrine) and weighed 20 kg, which equates to 6.30 mg/kg. Interestingly, this patient's vital signs (oxygen saturation, pulse, blood pressure) remain stable throughout dental treatment, as indicated in the sedation record, and the patient had all dental treatment completed by 12:00 p.m. However, at 12:05 p.m., the operating dentist administered 0.4 mL (0.16 mg) naloxone. It is because of this use of naloxone that this sedation was considered to have data indicative of an adverse event. A thorough analysis of the sedation record further revealed that the patient's

tonsils were categorized as Brodsky Scale 3+, and that the patient was characterized as having a history of snoring.

In another sedation record indicative of prolonged sedation and/or excess sedation, a 4 year, 5 month old female patient received five sextants of dentistry in 80 minutes. The patient had 72 mg of lidocaine (in solution as 2% lidocaine with 1:100,000 epinephrine) and weighed 14.54 kg, which equals 4.95 mg/kg. At one point in the sedation, this patient had an oxygen saturation without crying or sleeping of 98, and had stable vital signs throughout dental treatment. However, the patient remained “extremely sleepy” after dental treatment was completed and had “no lip color”. Accordingly, the patient subsequently had to be placed on oxygen three times in the post-operative period.

Similarly, in another sedation record, a 4 year, 2 month old male patient received two sextants of dentistry in 72 minutes. The patient had 36 mg of lidocaine (in solution as 2% lidocaine with 1:100,000 epinephrine) and weighed 15 kg, which equates to 2.40 mg/kg. This patient had an incidence of nausea/vomiting, post-operatively shortly after the dental procedures were completed (in office). The patient looked pale and required supplemental oxygen, a wet towel, and ammonia to wake him up. The patient required prolonged monitoring, and had a dismissal time of 123 minutes.

Lastly, one sedation record revealed an incidence of intraoperative nausea/vomiting. In this sedation record, an 8 year, 5 month old male patient received three sextants of dentistry in 70 minutes. The patient had 108 mg of lidocaine (in solution as 2% lidocaine with 1:100,000 epinephrine) and weighed 25 kg, which equates to 4.32 mg/kg. This patient vomited during the dental procedures (a.k.a. intraoperative

vomiting) during a period when the patient’s behavior fluctuated between quiet and crying. The accompanying hand written notes additionally read: “Pt. threw up, lots of liquid.” The patient’s vital signs were stable throughout the dental procedures, and patient records are otherwise non-significant. Table 10 summarizes some of the key data regarding significant adverse events.

Table 10. Significant Adverse Events

Significant Adverse Events	Age (years)	Gender	Lidocaine administered (mg/kg)	Lowest oxygen saturation without crying or struggling	Details
True desaturation	2.1667	Female	8.29	87	SaO2 dropped to 95 at 10:25 a.m., and 87 at 10:30 a.m. Nitrous oxide turned off at 10:30 a.m. SaO2 continued to read 87 at 10:35 a.m., but returned to 99 at 10:40 a.m. Tonsils unable to visualize pre-op.
Prolonged sedation / excess sedation	3.75	Female	6.30	99	SaO2 during dental procedures were within normal limits. Dental procedures completed at 12:00 p.m. 0.4 mL (0.16 mg) naloxone administered at 12:05 p.m. Tonsils Brodsky Scale 3+. Snore.
Prolonged sedation / excess sedation	4.4167	Male	4.95	98	“Pt extremely sleepy after tx. completed... Pt. had to be placed on oxygen 3 times after complete due to tiredness. No lip color.”

Prolonged sedation / excess sedation	4.1667	Male	2.40	100	N/V, post-operative, in office: "Pt. threw up – looked pale – gave O2, used wet towel on forehead. Dr. _____ used ammonia salt to wake him up. Monitored for an hour. He was discharged he felt much better."
Intraoperative vomiting	8.4167	Male	4.32	n/a	Stable vital signs, but crying throughout procedures. Incidence of intraoperative vomiting with notes: "Pt. threw up, lots of fluid."

4.11 Recovery Time

The "recovery time" of sedated patients, calculated as the time from the completion of dental procedures until discharge from the private group practice APD/PPD, varied significantly. The mean recovery time was 37.58 minutes, with a standard deviation of 22.27 minutes, and a standard deviation of the mean of 1.57 minutes (n=201). The median recovery time was 35 minutes. The minimum recovery time was 0 minutes, and the maximum recovery time was 137 minutes. A more detailed description of recovery experienced by patients can be found in Figure 15.

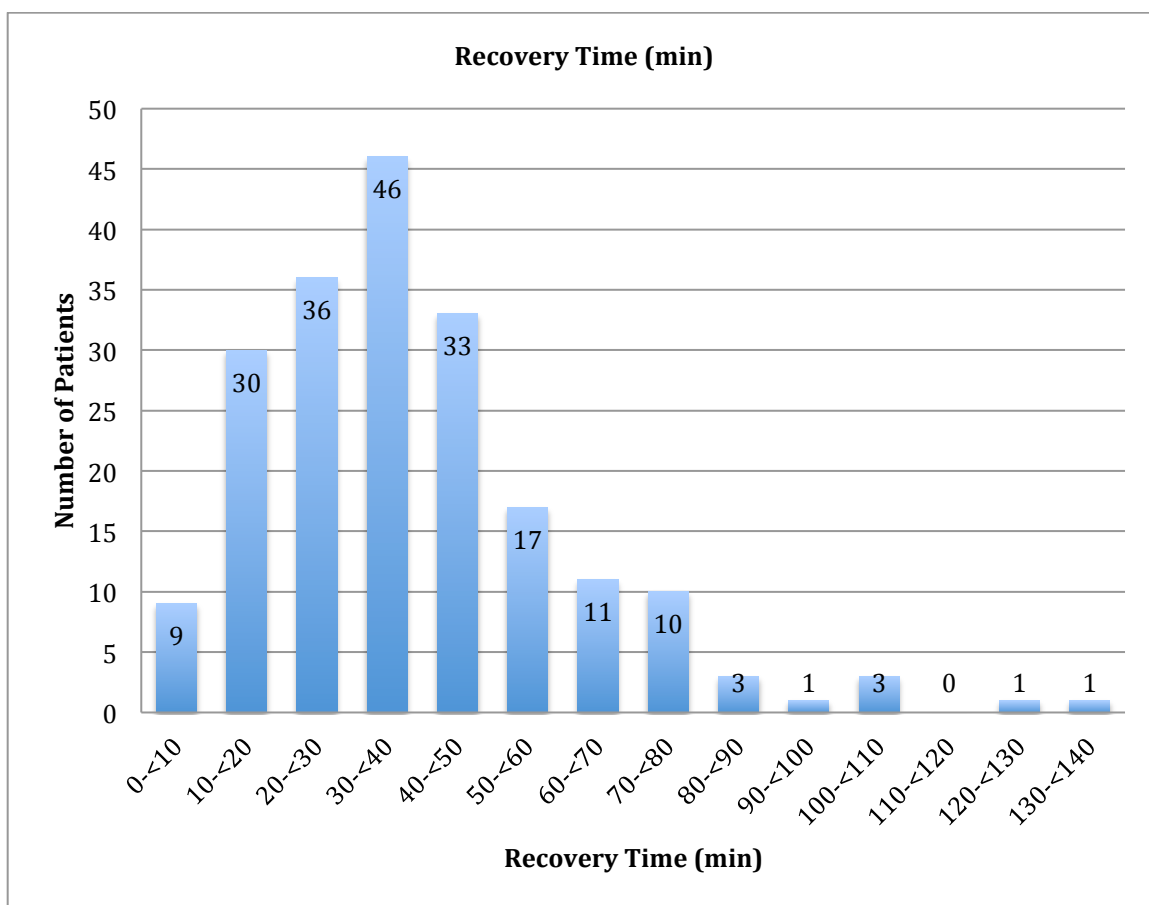


Figure 15: Recovery time (min)

4.12 Post-Operative Questions

As explained in section 3.2, APD/PPD protocol is for a follow-up phone call to be placed at 5 p.m. on the day of the sedation appointment, and a series of standardized questions are asked. The frequency that the answers to these post-operative questions were recorded, however, varied. For example, while data regarding post-operative nausea/vomiting was present for 270 patient records, data regarding being “tired” post-operatively was only present for 216 patients. A summary of the answers to post-operative questions can be found in Table 11.

Table 11. Answers to Post-Operative Questions

	Yes	No	% Yes
Able to eat and drink (n=267)	255	12	95.5%
Napped (n=266)	123	143	46.2%
Tired (n=216)	81	135	37.5%
Fluids only (n=222)	79	143	35.6%
Nausea/vomiting (n=270)	29	241	10.7%
Pain/discomfort (n=267)	26	241	9.7%
Stomach hurts (n=264)	16	248	6.1%
Bleeding (n=255)	12	243	4.7%
Breathing Problems (n=253)	0	253	0%

5. DISCUSSION

P.O. morphine is commonly utilized in pediatric medicine for pain management in cancer patients and patients with sickle cell disease, as well as for other conditions or situation where analgesia and/or sedation is desired.^{34, 61-65} A recommended dosage of IV morphine in critically ill children is found in the literature as 0.1-0.2 mg/kg/4-6 hr.⁶⁶ However, the maximum recommended dosage of morphine listed by Coté et al. in “Adverse Sedation Events in Pediatrics: Analysis of Medications Used for Sedation”, published in *Pediatrics*, is IV 0.025-0.1 mg/kg or IM 0.5-0.1.⁶⁷

The authors of this study did not find published guidelines for the maximum recommended dosages of P.O. morphine in children. Indeed, in an article on the use of oral morphine for the treatment of cancer pain in children, Hunt et al. highlight the lack of consensus in optimal dosing of morphine in children: “Although a number of studies

examine oral morphine pharmacokinetics in adults, evidence that relates to children of different ages is very limited. Consequently, wide variations exist (from 0.4 to 2.4 mg/kg/d) in recommended dosing schedules for the administration of oral morphine to children.”⁶⁸

When evaluating 0.66 mg/kg of P.O. morphine as part of a moderate sedation regimen in pediatric dentistry, it would be insightful to estimate the equipotent mg/kg dosage of the more commonly utilized P.O. meperidine. With this in mind, we attempted to extrapolate estimated maximum recommended dosages from opiate equianalgesic tables.⁶⁹⁻⁷¹ However, as Shaheen et al. point out, opiate equianalgesic tables exist in multiple forms, and “Variable equivalence ranges, within or between different equianalgesic tables, likely result in confusion and inaccurate opioid conversion and rotation.”⁶⁹ Indeed, while calculated dose ranges are a significant discussion point, the exercise of doing so may be inherently flawed. Shaheen et al. continues: “Computations, rather than data from clinical trials, are sometimes used to estimate or infer the potency ratios between opioids. Such derived ratios are devoid of clinical context and might be grossly inaccurate.”⁶⁹ Nonetheless, equianalgesic tables estimate that 0.66 mg/kg P.O. morphine would be roughly equivalent to 3.96– 6.6 mg/kg P.O. meperidine.⁶⁹ It should be noted, however, that these estimations were based on tables that related 24-hour opiate requirements despite being largely derived from “single-dose studies, expert opinion, and studies in noncancer patients”.⁶⁹ Although clinical studies comparing P.O. morphine in children with other opiates are sparse in the literature, one double-blind study of the analgesic efficacy of oral transmucosal fentanyl citrate and oral morphine in pediatric

patients utilized 0.6 mg/kg morphine, and stated that this dosage was an equivalent analgesic dosage to 10 µg/kg transmucosal fentanyl.⁶⁵

Equianalgesic tables are also capable of relating P.O. morphine to parenteral morphine. The ratios provided similarly differ depending on the source: according to such tables, 0.66 mg/kg P.O. morphine is equivalent to 0.11-0.33 mg/kg parenteral morphine.⁶⁹ While Shaheen et al. have questioned the accuracy of these equianalgesic tables,⁶⁹ the dosage range of 0.11-0.33 mg/kg parenteral morphine nonetheless exceeds the maximum dosage recommended by Coté et al. of 0.1 mg/kg.⁶⁷ With all of these considerations in mind, it is the opinion of the authors of this paper that the addition of 0.66 mg/kg P.O. morphine to a moderate sedation regimen should be utilized prudently and judiciously. Furthermore, while the intended level of sedation when using 0.66 mg/kg P.O. morphine is moderate, the greater dosage of opiate compared to what has historically been used in pediatric dentistry increases the risk of bringing the patient to a deep state of sedation.

While the use of hydroxyzine in combination with sedative agents such as meperidine, chloral hydrate, and midazolam have been well documented, dosages utilized in the dental literature vary considerably.^{11, 12, 40, 72-74} As discussed in section 2.4, Faytrouny et al. relate: "...dosages and schedules for oral administration of hydroxyzine have varied widely in clinical reports, ranging from 20 to 60 mg taken 45 min to 1 h before treatment... Some studies suggest that [the] weight of the child must [be] taken into account and 3.7 mg/kg dosage must be given."³⁸ Both Faytrouny et al. and Shapira et al. discuss the problems associated with assigning flat dosages to patients, namely that dosages in mg/kg will be higher in low weight patients and lower in high weight

patients.^{38, 40} This phenomenon is responsible for the relatively broad distribution of dosages of P.O. hydroxyzine administered to patients in mg/kg seen in Figure 6.

The authors of this study were unable to find any articles in the dental literature where ibuprofen was utilized as a component of a P.O. moderate sedation drug regimen. Accordingly, the addition of 100 mg of P.O. ibuprofen (flat dose) to 0.66 mg/kg P.O. morphine and 25 mg P.O. hydroxyzine (flat dose) represents a unique addition to P.O. moderate sedation drug regimens in pediatric dentistry. However, studies on pre-emptive administration of ibuprofen prior to primary tooth extraction have suggested this practice may have pre-analgesic effects in alleviating post-operative dental pain.^{46, 75} In *McDonald and Avery's Dentistry for the Child and Adolescent*, the therapeutic dose for ibuprofen in children is listed as 4-10 mg/kg/dose, given in 4-6 hour intervals.⁴³ Comparing this dosage to those listed in Figure 7 reveals that therapeutic dosages (or greater) were administered to 304 out of 360 patients, or 84.4% of the time. Accordingly, the addition of ibuprofen likely contributed to some degree of intraoperative and/or post-operative analgesia.

Perhaps the most similar drug regimens found in the literature, compared to the drug regimen of interest of 0.66 mg/kg morphine + 25 mg hydroxyzine (flat dose) + 100 mg ibuprofen (flat dose), are those drug regimens utilizing both meperidine and hydroxyzine. As mentioned in section 2.2, the use of meperidine in moderate sedation drug regimens in pediatric dentistry is well documented,^{2, 11-18} and numerous studies specifically discuss drug regimens utilizing both meperidine and hydroxyzine.^{11, 12, 74, 76} Accordingly, it would be reasonable to compare the results from previous studies involving both meperidine and hydroxyzine with the results of this study.

One example of a study involving meperidine + hydroxyzine was published in 2005 in *Pediatric Dentistry* by Cathers et al.¹¹ This study compared two meperidine + hydroxyzine regimens used in conjunction with nitrous oxide and oxygen inhalation sedation.¹¹ More specifically, one regimen consisted of 0.5 mg/lb submucosal meperidine + 0.5 mg/lb of P.O. hydroxyzine (SM group), while the other consisted of 1.0 mg/lb P.O. meperidine + 0.5 mg/lb of P.O. hydroxyzine (OM group), and both were utilized 50% nitrous oxide and 50% oxygen.¹¹ This study concluded that both regimens “were found to be safe and effective for sedating uncooperative pediatric dental patients”, and that neither regimen was found to be significantly more effective or safer than the other.¹¹ Based on the equianalgesic tables discussed above,⁶⁹⁻⁷¹ the 0.66 mg/kg P.O. morphine utilized in the regimen of interest in our study is a greater dose of opiate. However, the 25 mg P.O. hydroxyzine (flat dose) utilized in the regimen of interest in our study was less than the 1 mg/lb (or 2.2 mg/kg) of P.O. hydroxyzine utilized in the Cathers et al. study in 357 out of the 360 records where data was collected (99.2%). Additionally, ibuprofen was not utilized in the Cathers et al. study.¹¹ A direct comparison of oxygen saturation readings and cardiovascular parameters between the Cathers et al. study and this study is not possible due to methodological differences. However, Cathers et al. do report that oxygen saturation “never dropped below 95% in any patient”¹¹, an event that occurred twice in 330 records where data was available (0.6%) in our study. Finally, it is noteworthy that the practicing dentists in the Cathers et al. study waited less time after initial administration of oral medications (30 minutes for the SM group, and 45 minutes for the OM group)¹¹ before starting the dental procedures than was the protocol at APD/PPD (60 minutes).

Another example of a study involving meperidine + hydroxyzine was published in *Pediatric Dentistry* by Chen et al. This retrospective study compared the cardiopulmonary parameters and descriptive data of two sedation regimens: Regimen I (1 mg/lb P.O. meperidine + 25 mg P.O. hydroxyzine [flat dose]) and Regimen II (5 mg P.O. diazepam [flat dose], 25 mg P.O. hydroxyzine [flat dose], and 1 mg/lb submucosal meperidine).⁷⁶ Among the conclusions of this study were: “3. All cardiopulmonary parameters were within normal limits. 4. Regimens I and II had similar cardiopulmonary effects on sedated pediatric dental patients.”⁷⁶ Unfortunately, a direct comparison of cardiopulmonary data from Chen et al.’s study with the oxygen saturation and cardiovascular data from the current study is not possible due to methodological differences. However, some comparisons between the Chen et al. study and the current study are possible. For example, the mean “length of dental sedation visit” determined by Chen et al. (regimen I=45 minutes and regimen II=52 minutes) was found to be less than the median “working time” determined in our study (70 minutes).⁷⁶ Conversely, the mean “time from the end of treatment to discharge” determined by Chen et al. (regimen I=14 minutes and regimen II=12 minutes) was found to be less than the median “recovery time” determined in our study (35 minutes).⁷⁶ Lastly, the mean number of “sextants in which dental treatment was performed” was 2.87 for regimen I and 2.7 for regimen II, both of which are less than the median “number of sextants of dentistry completed per sedation appointment” in our study (4 sextants).⁷⁶

The dental literature additionally contains reports of a drug regimen consisting of meperidine + hydroxyzine + chloral hydrate, utilized with or without nitrous oxide and oxygen inhalation sedation.^{12, 17, 74, 77-79} The addition of chloral hydrate with meperidine

and hydroxyzine is thought to have a synergistic effect on the overall depth of sedation, a “phenomenon exacerbated by the addition of local anesthetics”.^{17, 80} When combining these medicaments, a common dosage combination is 50 mg/kg chloral hydrate, 1.5 mg/kg meperidine, and 25 mg hydroxyzine (flat dosage).^{17, 74} In a retrospective study by Leelataweedwud and Vann, use of this regimen resulted in six adverse events in 195 sedation appointments, or approximately 3% of the time;¹⁷ these included 1 incidence of true apnea, 1 incidence of true desaturation (defined as “a pulse oximeter reading of SpO₂ below 95 percent while the patient is quiet and still”), 3 incidences of prolonged sedation, and 1 incidence of intraoperative vomiting.¹⁷ Although Leelataweedwud and Vann’s criteria for “true desaturation” was more strict than the criteria used in the current study, the overall incidence of adverse events in their study was greater even if we included all incidences of “pulse oximeter readings of SpO₂ below 95 percent while the patient is quiet and still” from our data. In a prospective study by Sheroan et al., an analysis of the same 50 mg/kg chloral hydrate, 1.5 mg/kg meperidine, and 25 mg hydroxyzine (flat dosage) drug regimen resulted in ten episodes of desaturation (defined as a pulse oximeter reading of SpO₂ below 90 for longer than 15 seconds “or when the capnograph read 0 for respiratory rate and EtCO₂ or no visual signs of breathing and no audible breath sounds via the precordial stethoscope were detected for longer than 15 seconds”) occurring in two out of sixteen patients (12.5%).⁷⁴ While this represents a higher incidence of desaturation, although the Sheroan et al. went on to note that no apneic events occurred, and: “No desaturation fell below 85%. After head repositioning by a chin lift, SpO₂ immediately returned to above 90%. No desaturation event exceeded 25 seconds. No physiologic signs of hypoxemia, such as blue skin, were observed.”⁷⁴ This

differs from the current study in that the true desaturation event recorded, where $\text{SpO}_2=87$, lasted for at least 5 minutes (from 8:25 to 8:30, see Table 10).

Although knowledge of drug interactions between narcotics and local anesthetics has been “first reported Smudski and co-workers in 1964”^{81, 82}, the risks of these drug interactions were primarily brought to attention in pediatric dentistry by Goodson and Moore in the early 1980s.^{80, 81} In “Risk Appraisal of Narcotic Sedation for Children”, Goodson and Moore strongly caution the clinician:

What is clear regarding the various mechanisms for local anesthetic/narcotic interaction is that convulsions are not only more likely to occur, but after convulsions begin, the effect of further acidosis severely complicates recovery. Cardiac arrest becomes more likely as pH and P_{O_2} decrease and P_{CO_2} increases. The necessity of positive pressure O_2 in treating local anesthetic-induced convulsions cannot be overemphasized.⁸¹

After a thorough review of animal studies and 19 case histories involving excessive dosages of narcotics and/or local anesthetics, Goodson and Moore concluded that:

When given alone, irreversible toxicity is seen when doses exceed the MRD by a factor of 3. When administered in combination, irreversible toxicities would be expected... at 150% of the local anesthetic MRD and 150% of the narcotic MRD. To maintain a similar level of risk for the combination therapy (toxic dose/ $\text{MRD} \leq 3$), the doses maximally recommended for the local anesthetics and narcotics need to be decreased to 50% of their respective MRD.”

This represents a conservative recommendation for combined use of narcotics and local anesthetics,⁸¹ and was published at a time when sophisticated monitoring techniques such as pulse oximetry and capnography were not commonplace in pediatric dentistry. Additionally, many of the case studies were related to drugs that are no longer recommended for use in pediatric dentistry (such as alphaprodine).⁸¹

The recommendations by Goodson and Moore remain noteworthy when evaluating the current study, however, especially given the 0.66 mg/kg dosage of P.O.

morphine and the variable (and often extreme) dosages of lidocaine administered to patients as outlined in Figure 9. More specifically, as discussed in section 4.5, 149 out of 355 sedation records (42.0%) were shown to have had lidocaine dosages administered that were exceeding the maximum recommended dosage advocated by the AAPD of 4.4 mg/kg.⁵⁶ Additionally, 149 out of 355 sedation records (4.5%) had lidocaine dosages exceeding the more widely recognized maximum recommended dosage of 7.0 mg/kg.⁵⁷⁻⁵⁹ Such a practice generally falls outside the recommendations by Goodson and Moore,^{80, 81} yet a reasonable degree of safety is demonstrated.

The incidence of intraoperative vomiting (0.3% of patients) and post-operative vomiting (10.7% of patients when data was available) in the current study warrants further discussion. Intraoperative and post-operative vomiting are infrequent but commonly reported adverse events, and can be related to both P.O. moderate sedation regimens¹⁷ and/or nitrous oxide and oxygen inhalation sedation.^{52, 83, 84} For example, Needleman et al. reported an incidence of intraoperative vomiting of 8.1% when using a P.O. moderate sedation drug regimen of 55 mg/kg chloral hydrate + 1 mg/kg hydroxyzine and nitrous oxide and oxygen inhalation sedation.⁸³ Conversely, Hasty et al. reported no vomiting with the use of a P.O. moderate sedation drug regimen of 50 mg/kg chloral hydrate + 25 mg hydroxyzine (flat dose) + 1.5 mg/kg meperidine.⁷⁸ The fact that nitrous oxide and oxygen inhalation sedation can contribute to vomiting is a confounding factor when evaluating nausea and vomiting, however. The AAPD “Guidelines on the Use of Nitrous Oxide for Pediatric Dental Patients” state: “Nausea and vomiting are the most common adverse effects, occurring in 0.5% of patients.”⁵⁰ Other sources in the literature report the incidence of nausea and vomiting related to nitrous oxide and oxygen

inhalation sedation at 1% - 10%.^{8, 85} The authors of this study were unable to locate a comparison study of vomiting related to morphine use versus vomiting related to meperidine use for the purposes of P.O. moderate sedation in pediatric dentistry. Notably, however, in a study on analgesic use in the emergency department by physicians, conducted by Silverman et al., parentally administered morphine was found to cause nausea significantly less than meperidine (0% versus 12.8%).²⁷

The “success” of a P.O. moderate sedation regimen in pediatric dentistry varies depending on the clinician. This gap in the dental literature was discussed in depth by Vargas et al. in 2007:

Views of what constitutes a successful sedation differ extremely between clinicians... Many tools and scales of measurement to assess pediatric sedation have been used in sedation studies. The behavioral research literature is replete with methods that offer detailed and complex mechanisms in which to assess efficacy and success of a given intervention. Such composite indices have included various: (1) self-report measures; (2) behavioral observation ratings; and (3) physiologic parameters... Scales used in studies with pediatric dental sedation have additional components that measure: (1) safety of the sedation; and (2) the child’s movement; (3) crying; and (4) physical resistance.⁸⁶

Furthermore, as Vargas et al. reveal, the use of protective stabilization or restraint is itself a factor in defining the success of a sedation by some clinicians standards.⁸⁶ While 67% of respondents in their study “felt that the need to employ restraint with sedation did not necessarily indicate that the sedation was inadequate or unacceptable”, 36% of respondents “defined a sedation as optimal if treatment was accomplished with no restraint” and 39% of respondents” felt that the use of persistent restraint rendered the sedation unacceptable.”⁸⁶ Such viewpoints are noteworthy given that the majority of patients included in the current study were placed in protective stabilization for the entirety of the dental procedures. In a review of 53 sedation studies by Vargas et al.,

however, 49% used papoose boards.⁸⁶ Similarly, in a study by Houpt, 75% of clinicians use some form of physical restraint during sedation.²

In the current study, sedated patients were quiet 72.08% of the time, crying 13.38% of the time, struggling 6.08% of the time, engaging in “other” activities 4.56% of the time, and sleeping 3.95% of the time. The detailed assessment of behavioral data approximately every 5 minutes using the (SL=sleeping, Q=quiet, C=crying, ST=struggling, or O=other) rating scale is a novel approach to behavioral assessment during sedation for the purposes of the completion of pediatric dental procedures. From this data, estimating that sedations in our study were successful approximately 76% of the time suggests that our P.O. moderate sedation drug regimen of morphine + hydroxyzine + ibuprofen is comparably successful to the two meperidine + hydroxyzine regimens discussed by Cathers et al. (63% successful for the submucosal meperidine group and 80% successful for the oral meperidine group).¹¹ However, while only 2 patients out of the 595 patients originally screened in our study had their sedation appointments cancelled due to patient behavior (0.3%, see figure 1), Cathers et al. report that 32% of patients in the submucosal meperidine + hydroxyzine group had to have dental treatment aborted, while 20% of the oral meperidine + hydroxyzine group had to have dental treatment aborted.¹¹

Additional research is currently needed on opiate drugs in pediatric dentistry. As discussed in section 2.2, meperidine has been increasingly scrutinized in the medical community,^{20, 30} a fact that has led to the restriction of meperidine from some hospital formularies.²³ This has already begun affecting the availability of meperidine to pediatric dentists, and has the potential to affect the everyday practice of pediatric dentists across

the country. In fact, a similar phenomenon was recently observed after the discontinuation of production of chloral hydrate, which had previously been an important medication for P.O. moderate sedation in pediatric dentistry.² According to the FDA, the decision to discontinue chloral hydrate was “solely a business decision” made by the sole manufacturer of the product, Pharmaceutical Associates, Inc.⁸⁷ Nonetheless, many of the pediatric dentists who had been utilizing P.O. moderate sedation drug regimens with chloral hydrate as a component are now being forced to search for alternative drug regimens. Furthermore, another opiate drug utilized in dentistry, codeine, has also recently come under scrutiny by the medical community.⁸⁷ More specifically, the concerns expressed by the FDA are that DNA variations in the cytochrome P450 2D6 required to convert codeine to morphine cause excessive amounts of morphine to be released into the blood in the so-called “ultra-rapid metabolizers”.⁸⁷ Such concerns certainly warrant further scientific studies regarding optimal use of opiate drugs.

6. CONCLUSION

Our study suggests morphine can be utilized as the opiate component of P.O. moderate sedation drug regimens in pediatric dentistry. More specifically, this study demonstrates that 0.66 mg/kg morphine + 25 mg hydroxyzine (flat dose) + 100 mg ibuprofen (flat dose), when utilized with nitrous oxide and oxygen inhalation sedation, exhibits a reasonable margin of safety when appropriate monitoring is used and rescue equipment is available. This is particularly significant because morphine offers unique advantages over meperidine, including a reduced risk of drug interactions and an increased use and acceptance among providers in the medical community. Maximum

recommended dosages of drugs, including local anesthetics such as lidocaine, should always be taken into consideration in P.O. moderate sedation drug regimens. Additional research is needed on utilizing opiate drugs such as morphine in P.O. moderate sedation drug regimens in pediatric dentistry.

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8. APPENDIX


8.1 Sedation Monitoring Sheet (Front)

[illegible]

8.2 Sedation Monitoring Sheet (Back)


<u>PRE-OPERATIVE REPORT</u>			
<u>SEDATION INDICATIONS</u>		<u>AIRWAY STATUS</u>	
<input type="checkbox"/> Age	<input type="checkbox"/> Extensive tx	<input type="checkbox"/> Mouth breather	<input type="checkbox"/> Snores
<input type="checkbox"/> Resistant	<input type="checkbox"/> Excess activity	<input type="checkbox"/> Hx sleep apnea	<input type="checkbox"/> Obese
<input type="checkbox"/> Hysterical	<input type="checkbox"/> Learning disab	<input type="checkbox"/> Congenital abn	<input type="checkbox"/> Chest clear
<input type="checkbox"/> Combative	<input type="checkbox"/> Mental disab	<input type="checkbox"/> Limited opening	
<input type="checkbox"/> Physical disab	<input type="checkbox"/> Immat dev	<input type="checkbox"/> Hypertrophic tonsils	
<u>MONITORS</u>		<u>RESTRAINTS</u>	
<input type="checkbox"/> Pulse oximeter	<input type="checkbox"/> Pre-tracheal steth	<input type="checkbox"/> Papoose board	<input type="checkbox"/> Mouth-prop
<input type="checkbox"/> BP	<input type="checkbox"/> EtCO2	<input type="checkbox"/> Assistants	<input type="checkbox"/> Parent
<u>DISCHARGE EVALUTION</u>			
<input type="checkbox"/> Ambulatory	<input type="checkbox"/> Time discharged		
<input type="checkbox"/> Airway	<input type="checkbox"/> Evaluation of sedation		
<input type="checkbox"/> Awake/alert	<input type="checkbox"/> Post-op instructions		
<input type="checkbox"/> Age-appropriate behavior			
<input type="checkbox"/> Bleeding controlled	Doctor signature _____		
<u>POST OPERATIVE REPORT</u>			
<u>YES</u>	<u>NO</u>	<u>YES</u>	<u>NO</u>
<input type="checkbox"/>	<input type="checkbox"/> Able to eat and drink	<input type="checkbox"/>	<input type="checkbox"/> Pain/discomfort
<input type="checkbox"/>	<input type="checkbox"/> Fluids only	<input type="checkbox"/>	<input type="checkbox"/> Stomach hurts
<input type="checkbox"/>	<input type="checkbox"/> Napped	<input type="checkbox"/>	<input type="checkbox"/> Vomiting/nausea
<input type="checkbox"/>	<input type="checkbox"/> Tired	<input type="checkbox"/>	<input type="checkbox"/> Bleeding
<input type="checkbox"/>	<input type="checkbox"/> Other: _____	<input type="checkbox"/>	<input type="checkbox"/> Breathing problems
Spoke to _____			
Time _____		Date _____	
Assistant _____			
<u>NOTES</u>			

8.2 Letter of Support (David M. Perry, DDS)




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Tel 510.521.1KIDS • Fax 510.522.8283

David M. Perry, D.D.S.
Pediatric Dentist, UCSF Associate Clinical Professor

January 6, 2011

To the Committee on Human Research at UCSF,

I am writing this letter to express my wholehearted support of the UCSF-affiliated research project entitled "Morphine Revisited in Pediatric Dentistry. A Retrospective Study of a Moderate Sedation Regimen of Hydroxyzine + Morphine + Ibuprofen." To this end, I have agreed to allow Principal Investigator Adam Shaffer and colleagues to have access to all applicable dental charts and records from my private practice pediatric dentistry office in Alameda, CA. I have additionally agreed to help facilitate this research project, as outlined in the study proposal submitted to the Committee on Human Research at UCSF, in any way I can.

I have discussed this research project at length with Adam Shaffer, as well as with the collaborating members of his research committee. From these discussions, I feel the project holds scientific merit, and will significantly add to the literature on moderate sedation drug regimens as they pertain to pediatric dentistry. More specifically, the primary drug regimen being studied (Hydroxyzine + Morphine + Ibuprofen) is a regimen I have administered to well over a thousand pediatric dental patients over a 30 year period, yet there continues to be a lack of scientific literature on these medications as they pertain to pediatric dentistry. By scientifically collecting data from these sedations and performing the appropriate analyses, this study would be making profound contributions to the dental literature.

I look forward to collaborating with Adam Shaffer, fellow members of his research committee, and with UCSF, on this proposed research project. Please feel free to contact me with any questions or concerns.

Sincerely,



David M. Perry, D.D.S.

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