Title page:

Title: A Comparison of Oral Sedation-related Events of Three Multiagent Oral Sedation Regimens in Pediatric Dental Patients

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Statement of the Problem:

Providing safe and effective dental care while managing patients' behavior of is a continuous challenge for pediatric dentists. Many resources are available for pediatric dentists to aid in guiding patients' behaviors in order to provide quality dental care. These tools range from non-pharmacological methods to more advanced techniques that include oral sedation and general anesthesia.[4] Recent changes in parenting styles have led to a shift in treatment preferences favoring pharmacological management.[5,6]

Conscious sedation is a state of drug-induced depression of consciousness in which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation.[4] There is no intervention necessary to maintain an open airway, and spontaneous ventilation is adequate while cardiovascular function is maintained.[4,7]

The purpose of sedation is to significantly reduce anxiety, provide analgesia and allows the delivery of safe and successful dental treatment that may otherwise would be compromised.[8] This prevents negative experiences for the patient, the family and the dental team. It is also used to encourage change in the child's behavior, to help children develop their own coping skills and to promote acceptance of the dental environment.[9]

Although oral sedation can be very beneficial in obtaining patient's cooperation and facilitating dental treatment, some limitations exist. A major draw back of oral sedation is the inability to titrate the medications to the desired effect

given and unpredictability due to variable individual absorption and first pass effects.[2-3,7,10] The adverse events associated with oral sedation can occur during at any time, from the time of administration of medication, during the sedation procedure itself, and after the patient has been discharged from the controlled and monitored environment of the health care facility.[6] Nausea and vomiting are frequently seen when using sedation agents. Adverse events like frequent sleeping, gastrointestinal side effects, diminished activity, residual central nervous system alterations, respiratory depression and the existence of a paradoxical reaction were also observed in the literature.[11,12] Some of the most dramatic adverse sedation related events that have been reported are brain damage and death mainly due to respiratory depression in the sedated patients secondary to over sedation and the unintentional introduction of general anesthesia.[13]

A wide array of medications can be used in oral sedation. One drug regimen in use is a "triple-agent cocktail" that combines Midazolam (MZ), Meperidine (M), and Hydroxyzine (H).[11,14] Although several authors have claims of safety and efficacy of the MZ/M/H triple-agent cocktail, some concerns with use multi-agent regiments sedative effect on children exist. Use of multi-agent regimens may lead to a synergistic effect of all medications that potentially prolong the duration of the sedative effect which can be highly inconsistent and unpredictable.[11] This study will compare the adverse sedation-related events among three different sedation regimens (MZ/M/H, MZ/H, and M/H) in order to provide pediatric dentists with data that will aid them in their efforts to minimize adverse events during sedation

and using the least amount of medication necessary to provide quality dental care. It will also assess the potential adverse effect over time among the three regimens.

Introduction:

Cooperation is imperative to successful treatment in the pediatric dental patient. While the majority of children are able to cooperate with the use of non-pharmacologic behavior guidance techniques, such as tell-show-do, positive reinforcement and modeling that are carefully selected for each child, a small but significant percentage of children are unable to accept dental treatment.[1,15] This is especially true for pediatric patients under five years of age, who commonly fall into this category and can be some of the most difficult patients to manage.[4] These difficulties in management and absence of cooperation can be due to lack of psychological or emotional maturity and/or the existence of a mental, physical, or medical disability.[4,15] Unlike an adult, a child does not understand that cooperation during treatment may produce faster and more favorable results.[3] Ultimately, the lack of cooperation can lead to a diminished quality of dental care or even injury to the patient. In addition to inherent difficulties in patient cooperation, changes in parenting styles and the decreasing acceptance by parents of assertive behavior management techniques, such as hand-over-mouth and protective stabilization (papoose board), have resulted in the continuing search by pediatric dentists for other methods for facilitating treatment of uncooperative young patients.[16] When behavior management strategies are unsuccessful, some form of pharmacological sedation or general anesthesia may be indicated.[1] High levels of dental disease in

the pediatric population, increasingly difficult child behavior and parent expectations support the need for sedation services.[10] Additionally because general anesthesia in a hospital environment is an expensive alternative, pharmacologic sedation in the dental office is is often selective as a more cost effective option if the provider has the necessary clinical anesthesia-related skills and if the patient's health/comorbidities allow its utilization.[13,16]

While oral conscious sedation enables the dentist to perform necessary dental treatment that may not, otherwise, have been possible, some risks do exist.[2] Drug responses are unpredictable and can produce a variable range of adverse outcomes.[3] Due to the presence of these adverse outcomes, the search for an efficacious sedative regimen with the least amount of risk to the patient continues. The Pediatric dental literature contains numerous reports on various medications that have been administered alone or in combination for children as oral sedation.[8-11,14] Some examples include, but are not limited to, nitrous oxide, opioids, barbiturates, antihistamines, chloral hydrate and benzodiazepines.[9,18] Some of the commonly used medications for oral sedation in pediatric dental patients that can be used individually or in combination are Midazolam (Versed), Miperidine (Demerol) and Hydroxizine (Vistaril).

The efficacies of the (MZ/M/H) drug regimen during treatment have been investigated.[14,19-20] However, when choosing a drug regimen, it is important to not only look at the efficacy of the regimen, but also check its risks for adverse events. Adverse events can happen not only during treatment, but also from the time the drug administration prior to treatment, as well as after the patient has been

discharged from the health care facility.[11,14] Understanding of events occurring after discharge may influence future sedation protocols or discharge criteria and add a margin of safety if practitioners and parents are alert to them.

The purpose of this study is to compare the incidence of adverse sedation-related events for the three sedation regimens. The observation period will start at the time of drug administration and will continue until 24 hours after drug administration.

Review of Literature:

The concept of oral sedation use in pediatric dentistry is not new. Oral sedation involves using either a single medication or combination of drugs to achieve a state of altered consciousness in order to obtain a child's cooperation, reduce anxiety, provide analgesia and allow the delivery of safe and quality dental care.[8-9] For over 30 years oral sedation has been used in dental practices all across the country.[12] In a survey in 1988, the authors found that as many as 76% of surveyed pediatric dentists indicated that they used oral sedation in their practices.[21] Another survey in 1996 of 1,758 AAPD members reported using oral sedation 1 to 5 times every week, with 20% using it even more than 5 times per

week.[22] A more recent survey by Houpt comparing previous surveys taken in 1985, 1991, and 1995, found an increased use of sedation by pediatric dentists in the year 2000. This survey showed the total number of patients sedated with agents other than nitrous oxide in a three-month period had substantially increased in the year 2000, with 77,112 sedations conducted in that year, as opposed to only 33,683 in the year 1985.[18]

Various factors have led to the recent popularity of pharmacological, or advanced, management techniques in dental treatment of children. One factor is related to changes in parenting styles that led to a shift in treatment preferences favoring pharmacological management. In a study by Eaton et al. in 2005 found that parental acceptance of general anesthesia and sedation has increased over time. In their study, sedation was ranked as the fifth most acceptable behavior management technique after tell-show-do, nitrous oxide, general anesthesia and active restraint.[5] A more recent study by Patel in 2016 evaluating parental attitudes toward advanced behavior guidance techniques used in pediatric dentistry reported that oral sedation was rated as the most acceptable advanced technique in a survey of 105 parents, followed by general anesthesia.[6] Other possible consideration for favoring oral sedation include limited access to hospital operating rooms for general anesthesia, or GA. [5,13,16] General anesthesia has some disadvantages that may decrease its popularity. This is illustrated by Camm et al. who found that while children who had dental treatment under oral sedation and general anesthesia both experienced behavioral changes, those under general anesthesia were reported to have significantly more stress.[23] Another limitation with general anesthesia is possible

adverse anesthetic drug reactions, as demonstrated by Becker et al. who concluded that 10-20% of hospitalized patients experience such reactions his study.[24]

Oral conscious sedation is also not without risks. Two serious complications of oral sedation are respiratory suppression or depression and airways obstruction, which can lead to brain damage or death.[2,25] In a systematic investigation performed by Cote and colleagues, the authors investigated adverse events with regard to the medications used in sedation. In 28 of the 95 cases, death or permanent neurologic injury was associated with drug overdose.[20] Deaths and injuries after discharge were more commonly associated with sedatives with long half lives of elimination, often chloral hydrate but pentobarbital, promazine, promethazine, and chlorpromazine have also been reported. These medications with prolonged half lives account for nearly 80% of the devastating adverse events reported. They found no relationship with regard to outcome and drug class (opioids; benzodiazepines; barbiturates; sedatives; antihistamines; and local, intravenous, or inhalation anesthetics) or route of administration (oral, rectal, nasal, intramuscular, intravenous, local infiltration, and inhalation). Additionally, the authors reported that respiratory compromise accounted for most of the deaths/injuries that occurred in automobiles or at home after a procedure. Some children were injured in their car seats on their way home after a procedure. A possible mechanism for the injury was the child falling asleep with the rhythmic motion of the automobile and the head falling forward, thereby obstructing the upper airway. In the presence of residual drug effect, the child may be unable to aroused or be unable to reposition the head to relieve the airway obstruction.[20] This highlights a major concern with

oral sedation, which is the child who falls asleep in the car seat, can develop airway obstruction due to head and tongue position. The child is unable to spontaneously correct their position and unobstruct, which can lead to devastating outcomes.[26]

Other perhaps less serious but more common complications of sedation include allergic reaction, lethargy, nausea and or vomiting, behavioral changes, headaches, balance and gait disturbances, sleep disturbances, nightmares, hallucinations and ear pain. Some patients may experience nausea and vomiting while under the influence of oral sedation.[2,12] In other patients, certain medication, e.g. Midazolam, may activate paradoxical side reaction that results in yelling and fighting.[27-28] Some of the drugs used in may also induce gastro-intestinal issues such as diarrhea.[29] A 2010 study by Heard et al. found the prevalence of nausea and vomiting to be 8.8% and hemoglobin desaturation to be 6% during conscious sedation for dental procedures in 102 children aged 2-4 years. The authors used one of four regimens that include midazolam alone or in combination as follows: oral MZ (1 mg/kg), intranasal (0.7 mg/kg), intranasal MZ (0.5 mg/kg) with oral transmucosal fentanyl citrate, intranasal MZ at 0.3 mg/kg with intranasal sufentanil.[30] In addition to complications described earlier, dental procedure and use of local anesthesia can result in pain and/or lip, cheek or tongue biting.[12] Martinez and Wilson examined adverse events within the 24 hour post sedation period in 30 children aged 2-5 years. Parents were called 24 hours after the sedation and given a questionnaire. This pilot study compared Combination of CH (20.0-30.0 mg/kg), meperidine (1.0-2.0 mg/kg), and hydroxyzine (1.0-2.0 mg/kg) to midazolam alone (0.5-0.75 mg/kg). The authors demonstrated that children sedated

for dental procedures with a triple combination of chloral hydrate, meperidine and hydroxyzine were more likely to sleep on the drive home and were more difficult to wake than children sedated with midazolam alone. Only 20% of the patients reported post operative pain, 30% reported having a “fat lip, cheek or jaw”, and none vomited. There was no difference between the two regimens in terms of postoperative pain, vomiting, eating, evening sleep or memory.[31] A prospective study by Huang et al. comparing combinations of a narcotic, a sedative-hypnotic, a benzodiazepine, and/or an antihistamine found that that post-discharge excessive somnolence during transit and while at home as well as nausea and vomiting were frequent complications with oral sedation. Specific findings from this study include that 60.1% of patients slept in the car on the way home, while 21.4% of that group was difficult to awaken upon reaching home. At home, 76.1% of patients slept. Additional findings were that 85.7% of patients who napped following the dental visit slept longer than usual. After the appointment, 19.6% exhibited nausea, 10.1% vomited, and 7.0% experienced a fever.[31]

Currently, various oral sedation regimens exist. This is largely because of the the different types of drugs that can be used alone, or in conjunction with other drugs, to create a diverse range of outcomes and side effects. Narcotics, antihistamines and benzodiazepines have all been used separately, and in combination, in an attempt to find the ideal sedation regimen which could be used for most clinical situations.[33] However, no single agent or regimen has yet to be recognized as the standard for dental procedures.[16] The ideal oral sedation regimen is one that would provide safety for the patient, minimum respiratory depression,

adequate sedation, minimal patient movement, early and rapid onset of drug reaction, and adequate working time.[33]

Complicating the process of determining the optimal oral sedation regimen are the different needs of each patient as well as the different drug interactions within each patient. Typically, the less cooperative a patient, the stronger the regimen that is required to accomplish the desired sedation level by the dentist. The stronger regimens are often created by mixing different medications together, allowing dentists to target patients' specific needs taking advantage of the synergistic effect of combining these drugs.[34-36] The increase in the strength in the form of mixing different drugs may, however, lead to an increase the likelihood for adverse effects.[20,25,31] This is shown in an investigation by Cote et al. who found that the use of three or more sedatives was strongly associated with adverse outcomes (18/20) as compared to one or two medications (7/70), even when given within acceptable doses.[25] An important point to consider when using oral sedation medication is that adverse reactions can occur at multiple time points during the oral sedation appointment. Adverse events can be seen immediately after administering the oral sedation medication, before, during and after treatment has been completed.[20] A major risk with using multi-drug regimens is the possible increased sedative effect of such regimens which might extend the working time of the drug beyond the time needed for completion of dental treatment. In these cases, patients who appear awake during treatment may become excessively sleepy and drowsy after stimulation has ceased, thereby rendering them more deeply sedated after the procedure is over. This creates a risk for adverse events after discharge

and they are no longer under the direct supervision of trained clinicians.[25,31] This is illustrated by the previously mentioned critical review by Cote and colleagues in which they reviewed 95 adverse sedation events in pediatric patients using critical incident analysis of case reports. The authors found that nearly 80% of the events presented initially as respiratory depression. Additionally, negative outcomes were associated with multiple drug combinations and interactions. Dental specialists had the greatest frequency of adverse sedation related events when associated with the use of 3 or more sedating medications.[25]

Historically, Chloral hydrate, CH, has been a main component in the triple combination, or cocktail, sedation medication, along with hydroxyzine and Meperidine.[7,11,32] A recent and comprehensive retrospective review of 195 pediatric conscious sedations using multi-agents regimen containing Hydroxyzine, Chloral hydrate and Meperidine, as the following regimen CH/M/H: 50 mg/kg, 1.5 mg/kg,25 mg, reported that 72% of the sedations were satisfactory and that adverse outcomes were few and minor under a strict protocol and use of oxygen supplementation.[12] Despite the widely stated claims of safety and efficacy of this triple-drugs cocktail, there are expressed concerns with CH as a sedative agent for children.[14] The sedative properties of chloral are attributed to the active metabolite trichloroethanol. Alcohols, such as trichloroethanol, follow zero-order kinetics and have no definitive half-life, leading a to a prolong sedative effect that can reach up to 10 hours, while the inactive metabolite like trichloroacetic acid the half-life ranged from 89 to 94 hours.[37] Consequently, the duration of the sedative effect can be highly variable and unpredictable.[2] Since the half-life of chloral hydrate is fairly

long and variable, an extended period of observation for recovery is often required and residual effects may persist for up to 24 hours. More recently, Chloral Hydrate has been replaced with Benzodiazepines, mainly Midazolam. In a study by McCormack et al, the authors found that patients who took chloral hydrate had more somnolence and less talking, while those who took Midazolam had more difficulty walking and slurred speech. Most adverse events occurred within the first 8 hours of discharge. The authors compared combinations of CH/M/H (dosages of 30 mg/Kg, 2 mg/kg and 2 mg, respectively to MZ/M/H (doseages 1 mg/Kg, 2 mg/kg and 2 mg/Kg) in 40 children aged 3-6 years.[11] Similarly, Ritwik et al. reported comparable adverse effects 8 hours, and even up to 24 hours, after oral sedation in 46 children aged 3-9 years. The regimens compared were MZ/H (each with a dosage of 1-2 mg/Kg) compared to MZ alone (0.5-0.7 mg/Kg). They found that a significantly larger proportion of children in the meperidine and hydroxyzine group experienced prolonged sleep at home, while more children in the midazolam group exhibited irritability in the first 8 hours. They also reported no statistical differences between the 2 groups with respect to incidence of pain, fever, vomiting, sleeping in the car, snoring, and difficulty in waking up.[38] A 2011 study by Costa et al. compared post-discharge adverse events in 103 dental sedation in children aged 1-8 years who had received either high dose midazolam 1.0-1.5 mg/kg (maximum: 20.0 mg) or chloral hydrate70-100 mg/kg CH (maximum: 2.0 g) for dental sedation. In this study, 42 children had 103 dental sedations. Midazolam 1.0 mg/kg was used for the first sedation. If the child was cooperative, the same regimen was used for the subsequent sedation. If not, the dosage was increased to 1.5 mg/kg midazolam,

followed by chloral hydrate 70mg/kg and chloral hydrate 100 mg/kg as necessary. Intraoperative adverse events were recorded. In addition, caregivers were contacted 24 hours after the procedure and asked about thing such as agitation, nausea, vomiting, dizziness, sickness, difficulty breathing, irritation, hallucination, and excessive sleep. The most common adverse events were excessive sleep (41.9%) and hallucination (3.9%). Adverse events were more common with chloral hydrate than midazolam.[39] Another major disadvantage of chloral hydrate is that it does not have a reversal agent. Due to these disadvantages and the introduction of benzodiazepines and other agents, chloral hydrate is being used less frequently in general and not used in the pediatric dental clinic in Loma Linda University, therefore, it will not be included as one of the drugs in this study.

One drug regimen that has become more popular recently for the sedation of pediatric dental patients is a triple-agents combination that includes Midazolam, Meperidine, and Hydroxyzine (MZ/M/H)[8]. Midazolam is a water-soluble short acting, high potency benzodiazepine that provides sedative, anxiolytic, amnestic, and hypnotic effects. The oral peak onset is 10-20 minutes with a half-life 2.2 to 6.8 hours.[40] The major metabolite is α-hydroxymidazolam and is considered to be just as potent as midazolam.[40] Benzodiazepines are regarded as being extremely safe in clinical use, having a wide margin between therapeutic dose and toxic dose.[10] Midazolam, specifically, is considered one of the safest and most effective sedative drugs available.[41,42] Its successful use in the pediatric population is well documented in the literature.[41] Midazolam and other benzodiazepine act centrally at the gamma amino-butyric-acid (GABA) receptor in the limbic system to produce anxiolysis and

profound amnesia.[40] A major benefit of utilizing Midazolam is that it is easily reversed by flumazenil.[2,42] In A 2006 study by Sheroan et al, the authors compared behavior and physiological effects of two different sedation regimens; chloral hydrate, meperidine and hydroxyzine at doses of 50 mg/Kg, 1.5 mg/kg and 25 mg, respectively (regimen A) vs. midazolam, meperidine and hydroxyzine 1 mg/Kg, 1 mg/kg and 25 mg, respectively (regimen B). Sixteen children who needed two sedation appointments each were randomly assigned to receive one regimen for their first appointment and the other for the second appointment, a crossover design. No significant differences were found in terms of behavior or physiologic parameters between the regimens, however 10 episodes of hemoglobin desaturation in 2 patients were observed with regimen A, whereas no desaturation events occurred with regimen.[14] Midozalom has some drawbacks other very short working time when used alone. The main disadvantage to using midazolam is that some patients may develop paradoxical reactions characterized by restlessness, agitation, anxiety and sometimes aggressive behavior.[27] These children show an extreme inconsolable irritability and agitation, making treatment and discharge challenging.[28] A 2010 study by Lourenco-Matharu and Roberts examined adverse events during 510 pediatric dental sedations with midazolam (0.5 mg/kg). Overall, twenty three percent of children experienced side effects including crying/agitation (14.5%), hiccups (1.6%), diplopia (1.6%), and lip biting (1.2%). One child required reversal with flumazenil as “he appeared to be over sedated by sleeping deeply”. No serious adverse events occurred.[43]

Meperidine is a narcotic, specifically a synthetic opioid analgesic, that causes central nervous system (CNS), cardiovascular, and respiratory depression. It is commonly used to elevate the pain threshold to control moderate-severe pain. It is a mu receptor agonist that primarily produces analgesia and sedation that can lower seizure threshold and induce histamine release. Oral Meperidine analgesia can be obtained within 30 minutes of administration. Peak analgesia onset is 60-120 minutes with a half-life of 2.5 to 5 hours. Meperidine can be reversed by Naloxone. The recommended therapeutic oral dosage of meperidine for sedation is 1.1 to 2.2 mg/kg when given orally.[42,44-45] Meperidine is absorbed well by all routes but is less effective when given orally because only 50% of the drug escapes first-pass metabolism to enter the blood stream. However, the oral route is considered by most pediatric dentists to be the route of choice when sedating an uncooperative pediatric dental patient, and many believe the oral route to be the safest and associated with the least potential for overdose.[46-47] The side effects of Meperidine are many and varied and may be seen with a small dose as well as a large dose. They may vary from dizziness, anorexia, nausea and vomiting to flushing, perspiration, dry mouth or sleep. [42,44-45] Convulsion has been reported as one of the possible side effects of using Meperidine, comorbidities were mainly reported in patients with renal impairments which suggested to be related to the accumulation of the inactive metabolites (normeperidine).[47]

Hydroxyzine is a long acting H1 antagonist providing antihistamine, antipruritic, and antiemetic properties. Hydroxyzine is considered a sedative, CNS depressant and may provide relief from anxiety, itching, skeletal muscle relaxation,

analgesia, and bronchodilation and antiemetic effects. Hydroxyzine when given orally has an onset of 15-30 minutes.[48-50] It has been used in conjunction with chloral hydrate, midazolam, and meperidine to reduce the incidence of nausea and vomiting.[50] It does not cause respiratory depression when used in the recommended doses and there are no known side effects. [48-50] The bronchodilatory effect of Hydroxyzine is in fact favorable during oral sedation.[25]

The use of Mz/M/Hx in different combinations has been described in the literature.[11,14,51-52] In a retrospective study conducted by Lanehan et al, the authors reviewed 248 Pediatric Oral sedations utilizing the combination of Meperidine and hydroxyzine for dental treatment. All dosages were within the recommended guidelines for both drugs. The maximum dosage of meperidine administered was 2.2 mg/kg with a maximum dose of 50 mg (ranging from 1 mg/kg to 2.2mg/kg). Hydroxyzine was typically administered in 12.5 mg increments, ranging from 0.5 mg/kg to 2.2 mg/kg with a maximum dose of 50 mg. The authors reported that over 81% of sedations were considered effective or very effective. While Less than 5% of sedations were aborted due to behavior.[51] When comparing midazolam alone (0.5 mg/kg)

and in combination with Hydroxyzine (3.7 mg/Kg and MZ 0.3 mg/kg) in 56 dental sedations, Shapira at al. found that the Midazolam group exhibited significantly more movement in the first 20 minutes. They also found that during the first 30 minutes of treatment, more children cried in the Midazolam group, while the combination group presented more children asleep or quiet. No significant differences were found in behavior as a function of the order the sedative regimens

were given. Overall success was similar in the two regimens.[33] A prospective study by Musial et al. compared the use of Midazolam alone (1 mg/ kg)and in combination with Meperidine 1 mg/kg, MZ: 0.5 mg/Kg) and found that no difference in physiology or behavior between the groups. However, higher heart rates and disruptive behaviors occurred more frequently during or after local anesthesia administration in this crossover design study of 20 children aged 3- 5 years.[53] In a study by Dosani et al, the authors investigated combinations of midazolam, hydroxyzine, and meperidine orally or intramuscularly in 50 children aged 2-16 years of age. They found that 66% of children slept in the car; of these 12% were difficult to awaken. Agitation was observed in 22%, restlessness in 10%, withdrawn behavior in 16%, and soft tissue trauma in 18%. Motor imbalance and restlessness was significantly associated with midazolam. Eighty-two percent slept between discharge and bedtime, with 16 % sleeping for greater than four hours.[52]

As discussed previously, the sedative action of oral sedation medications is potentiated when different medications are combined. The action is either synergistic or additive in its effect. Much of the sedation research does not address the rates of agitation, irritability, intra- operative and post-operative behavior.[11,38] Few studies have been published which investigate events that may occur within 24 hours of a sedation. [11,38] Adverse events might be expected from the time of drug administration to the beginning of treatment, throughout the treatment, during early recovery while in the office, and after discharge from the office. Failure to properly monitor the patient might lead to early discharge prior to being fully recovered, which results in experiencing adverse events at home. This study will

compare the post sedation events from three different multidrug oral sedation regimens in order to help pediatric dentists determine the best course of action for their patients and prepare parents appropriately and caution them about the expected effects. Patients will be evaluated for adverse effects within two time periods at 8 and 24 hours post oral sedation procedure.

Materials & Methods:

In this randomized clinical trial, a sample of 60 healthy (ASA I) patients will be studied, with 20 patients randomly distributed for each group primarily. Sample size selection was made based on power analysis and previous studies [8].

These patients are scheduled to undergo oral sedation appointments in a pediatric dental clinic for treatment, which involve no more than two quadrants of dentistry. These patients have been scheduled for oral sedation due to situational anxiety in the dental operatory and will range from 3-6 years of age with no gender, race or ethnic restrictions. Exclusion criteria will leave out children who have taken any medication within the two weeks prior to dental treatment, those who presents for emergencies, those who have been sedated previously by other providers or in other institution, those with a BMI greater than the 95th percentile for their age and gender, and those who fail to drink the entire amount of medication dispensed.

Informed consent will be obtained upon arrival for their sedation appointment. The standard sedation protocol and guidelines of the AAPD and will be followed in each case. For this study Group 1 will be given the triple combination of Midazolam, Meperidine, and Hydroxyzine (MZ/M/H) at a dose of 0.5-0.75 mg/kg, 1.5-2mg/kg, and 1.5-2 mg/kg respectively. Group 2 will be given the double combination of Midazolam and hydroxyzine (MZ/H) at a dose of 0.5-0.75mg/kg and 1.5-2mg/kg respectively. While group 3 will receive Meperidine and Hydroxyzine (M/H) at a dose of 1.5-2mg/kg each. On the day of the sedation, the child will be weighed, and the oral medications will be dispensed as described after fasting status is confirmed. If the child refuses to drink the medication from a small cup, the medication will be administered by feeding syringe with the parents' assistance. Nalaxone will be used as a reversal agent for Meperidine and it will be used in a calculated doses of 0.1 mg/kg with maximum dose of 2 mg. Flumazenil will be used as a reversal agent for Midazolam and it will be used in a calculated doses of 0.01mg/kg with maximum dose

of 0.2 mg. Reversal drug doses will be set out for use if needed. Nitrous oxide/oxygen (N_2O/O_2) will be used in all sedations (50% N_2O/50% O_2 during local anesthetic administration and 30% N_2O/70% O_2 during the remainder of treatment) with 100% O_2 given for five minutes pre and post-operatively. Patients will be monitored continuously using a pulse oximeter which provides a reliable estimate of O2 saturation of the patient. Detection of airway obstruction and apnea based on reduction in O2 saturation. A precordial stethoscope will be used to monitor airway patency throughout the procedure, and visual observation of respiratory function. Blood pressure and heart rate will be monitored and recorded automatically every fifteen minutes throughout the procedure. Xylocaine (2% lidocaine with 1:100,000 epinephrine) will be used for local anesthesia in all cases and the total amount given will not exceed 4mg/kg lidocaine. Discharge information and post-operative care instructions, including emergency numbers will be given to the parents prior to discharge.

The dentist performing the sedation will receive a questionnaire (Survey 1) regarding the period of time from administration of medications up until discharge (Appendix 1). In addition, parents will be instructed to fill out two other surveys regarding events and they will receive two phone interviews for data collections. These surveys will be filled out at 8 hours (Survey 2) and 24 hours (Survey 3) after discharge by the parents (see appendix 2 and 3). The phone interview will be performed at the provider convenience to collect the data which will includes the answers for the survey's questions. Surveys consist of questions falling into the following categories: (1) amount and frequency of sleeping; (2) discomfort; (3) food

intake; (4) changes in sleep rhythms; (5) incidence of nausea or vomiting; and (6) incidence of paradoxical reaction.

Statistical Analysis:

The purpose of this study is to compare the incidence of adverse sedation related events between three different multi-agent oral sedation regimens in pediatric dental patients. Data will be collected in the form of 3 survey sets: the surveys is survey set 1 are written surveys to be completed by the dentist (Survey 1), and survey sets 2&3 are phone surveys to be conducted by the researcher with the parents regarding the adverse effects that may occur after 8 hours (Survey 2) and 24 hours (Survey 3) after discharge. The majority of these survey responses fit into predetermined categories. These categories will be compared between the different drug regimens, and also between the different survey sets.

Category	Related Question Numbers
Paradoxical Reactions	Survey1: 5, 6, 7, 8 Survey 2: 1, 2, 3, 4 Survey 3: 1, 2, 3, 4
Sleep disturbances (sleepy)	Survey 1: 15 Survey 2: 5, 7,10 Survey 3: 5, 8
Behavior changes	Survey 1: - Survey 2: 11,12,13, Survey 3: 9, 10, 11,23
Respiratory effects	Survey 1: 9,10,11,12 Survey 2: 5b-c Survey 3: 5b-c
CNS Effects	Survey 1: 15, Survey 2: 5d,14, 15, 18,19 Survey 3: 5c, 5d, 6,7,12,14,16,17,18,19,
Gastrointestinal Upset	Survey 1: 2, 3, 4 Survey 2: 19, 20, 21, 22, 25

	Survey 3: 17,18,19, 20, 24
Amnesia effect	Survey 2: 16,17 Survey 3: 14,15
Physical reaction	Survey 1: 14 Survey 2: 24,25,26 Survey 3:22,24, 25,

All responses will be entered into an excel spreadsheet and analyzed using SPSS 16 (SPSS Chicago, IL). Data Analysis will include descriptive and inferential statistics. The inferential statistics will include incident rate ratios analysis, chi square and one-way ANOVA . The significance level will be set as p less than 0.05.

Appendix 1

(Survey 1)

Patient # _____ Weight _____ Dentist # _____

Patient Age _____ Height _____ Date of TX _____

Regimen Administered _____ MZ/M/H _____MZ/H M/H_____

Operating Dentist Survey

Did the patient…		Yes	No
1. Drink the medication without difficulty?			
2. Complain of nausea?	Pre / During / Post		
3. Vomit	Pre / During / Post		
4. Complain of upset stomach	Pre / During / Post		
5. Cry or scream inconsolably?	Pre / During / Post		
6. Exhibit any abnormally aggressive behavior?	Pre / During / Post		
7. Bite or scratch anyone?	Pre / During / Post		
8. Seem hyperactive?	Pre / During / Post		
9. Require the use of reversal agents? Which one?	Pre / During / Post		
10. Saturation level ever drop below 95?	Pre/ During/ Post		
11. Saturation level ever drop below 90?	Pre / During / Post		
12. Require Head Repositioning?	Pre / During / Post		
13. Slur or have difficulty speaking?	Pre / During / Post		
14. Have any abnormal rash?			
15. Sleep during treatment?			
a. Was the patient asleep at the end of treatment?			
b. Was the patient difficult to wake up?			
16. At any point was treatment aborted. (if yes, why?)			
At discharge, could the patient?			
17. Sit unaided?			
18. Hold their head up on their own?			
19. Speak age-appropriately?			
20. Walk on their own?			

Please comment on any "Yes" answers from above, providing additional detail

Notes:

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Appendix 2

(Survey 2)

Patient # _____ Dentist # _____ Surveyed _____

Patient Age _____ Date of TX _____ Survey Date _____

8 Hour Sedation Follow-up Phone Survey

After leaving the dental clinic, did your child….	Yes	No
1. Cry or scream inconsolably?		
2. Exhibit any abnormally aggressive behavior?		
3. Bite or scratch anyone?		
4. Seem hyperactive?		
5. Fall asleep on the car ride home?		
c. Does your child normally sleep in the car?		
d. Did your child snore?		
e. Does your child usually snore?		
f. Was it difficult to awaken your child when you arrived home?		
6. Act in a way that made you concerned and caused you to pull the car over?		
7. Sleep soon after arriving home?		
a. Did your child complain of bad dreams?		
8. Need help to sit up?		
9. Have difficulty walking?		
10. Seem lethargic?		
11. Play immediately after arriving home?		
12. Talk less than normal or refuse to talk?		
13. Talk more than normal?		
14. Slur or speak incoherently?		
15. Complain of or seem dizzy?		
16. Have any memory of what happened at the dental office?		
17. Talk about the dental appointment?		
18. Have or complain of a headache?		
19. Complain of nausea?		
20. Vomit?		
a. Did your child consume any liquids or foods before vomiting?		
21. Have an upset stomach?		
22. Have diarrhea?		
23. Take any medication?		
24. Have any abnormal rash?		
25. Have a hiccup?		
26. Did your child develop any fever?		

Did anything else happen that you feel is important to mention?

Notes:

_____

_____

Appendix 3

(Survey 3)

Patient # _____ Dentist # _____ Surveyed _____

Patient Age _____ Date of TX _____ Survey Date _____

24 Hour Sedation Follow-up Phone Survey

Since the 8 hour follow-up, did your child….	Yes	No
1. Cry or scream inconsolably?		
2. Exhibit any abnormally aggressive behavior?		
3. Bite or scratch anyone?		
4. Seem hyperactive?		
5. Sleep more or less than normal?		
a. Did your child snore?		
b. Does your child usually snore?		
c. Was it difficult to awaken your child?		
d. Did your child complain of bad dreams?		
6. Need help to sit up?		
7. Have difficulty walking?		
8. Seem lethargic?		
9. Play more or less than normal?		
10. Talk less than normal or refuse to talk?		
11. Talk more than normal?		
12. Slur or speak incoherently?		
13. Complain of or seem dizzy?		
14. Have any memory of what happened at the dental office?		
15. Talk about the dental appointment?		
16. Have or complain of a headache?		
17. Complain of nausea?		
18. Vomit?		
19. Have an upset stomach?		
20. Have diarrhea?		
21. Take any medication?		
22. Have any abnormal rash?		
23. Act in a way that made you concerned.		
24. Have a hiccup?		
25. Did your child develop any fever?		

Did anything else happen that you feel is important to mention? _____

Notes:

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