Title
A Retrospective Study of Chloral Hydrate vs. Midazolam Containing Triple Cocktail Oral Sedation in Pediatric Dentistry

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A Retrospective Study of Chloral Hydrate vs. Midazolam Containing
Triple Cocktail Oral Sedation in Pediatric Dentistry

by
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THESIS
Submitted in partial satisfaction of the requirements for the degree of
MASTER OF SCIENCE
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A Retrospective Study of Chloral Hydrate vs. Midazolam Containing Triple Cocktail Oral Sedation in Pediatric Dentistry

Anuhya Uppula, DMD

ABSTRACT

Purpose: To evaluate, retrospectively, the safety and efficacy of two moderate oral conscious sedation drug regimens used at UCSF Pediatric Dentistry Clinic: chloral hydrate, meperidine, and hydroxyzine (CH/M/H) versus midazolam, meperidine, and hydroxyzine (Mid/M/H).

Methods: Data was collected from sedation records from 7/21/2010 - 6/3/2015 at UCSF Pediatric Dental Clinic. The records were screened and those meeting inclusion criteria were analyzed for patient behavior, completion of treatment, and adverse events. Appropriate statistically analyses were conducted based on specific collected data set with P-value <0.05 to be significant different.

Results: Of the original sample of 1016 sedation charts, 295 met the inclusion criteria for analysis. There were 27 adverse reactions (vomiting, over-sedation, or desaturation) of which 16 were in Mid/M/H cases and 11 were in CH/M/H cases. There was no statistically significant difference between the two regimens in safety. The average behavior scale was closer to sleeping for CH/M/H cases whereas it was closer to crying/moving for Mid/M/H cases. However, there was a significant difference between the two regimens in efficacy. CH/M/H worked significantly better on children younger than 9 years of age. Resident operator experience did not significantly affect sedation outcomes. Moderately uncooperative patients had significantly better sedation results
with the CH/M/H regimen than with the Mid/M/H regimen. For fairly cooperative and extremely uncooperative patients, there was no significant difference.

**Conclusion:** There was a significant difference in efficacy between the two triple cocktail regimens, with the CH/M/H regimen showing better behavior outcomes and completion of treatment versus Mid/M/H regimen. There was no significant difference in safety between the two regimens. Per this study, as long as sedation guidelines are followed, the chloral hydrate regimen can be safely and effectively used in pediatric dental oral conscious sedation.
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1. INTRODUCTION

Completing dental work on anxious, fearful, and generally uncooperative children may require the pediatric dentist to utilize behavior management techniques, protective stabilization, sedation, or general anesthesia. Consecutive surveys by Houpt et al (1985, 1991, 1995, and 2002) demonstrated an overall increased use of sedation by pediatric dentists as more children of younger age having extensive caries.

Another contributing factor to increased sedations may include evolving parental styles. Parents of recent generation provide less disciplinary action and more indulgence leading to an increasing number of children that lack the coping skills necessary to contend with new experiences such as dental visits (Long, 2014) (Boyce, 2014) (Goleman, 2014) (Casamassimo, Wilson, & Gross, 2002). Parents are relying more and more on medical or psychological methods of management (Casamassimo, Wilson, & Gross, 2002) and are less likely to accept assertive behavior management such as passive restraint, hand-over-mouth (HOME) or voice-control (Eaton, McTigue, Fields Jr, & Beck, 2005) (Fields, Machen, & Murphy, 1984), which were widely used in the past. Pediatric dentists have thus adapted to the new generation of parents by utilizing advanced behavior guidance techniques such as sedation. A survey by (Adair, Waller, Schafer, & Rockman, 2004) reports 62% of pediatric dentists in the American Academy of Pediatric Dentistry (AAPD) reported to using oral conscious sedation.

Although oral sedation is a frequently used behavior guidance technique, there is a lack of agreement among practitioners on types and dosages of drugs used (AAPD Guidelines, 2011) (Houpt, 2002). Practitioners often state sedation is as much art as it is
science—they have to assess the child's temperament, medical history, and the extend of the treatment plan to select the type of medications as well as dosages that they feel would give the right outcome (Nathan, 2015). Due to the lack of consensus, a wide range of classes of drugs and dosages are used currently by pediatric dentists (Houpt, 2002) (Duncan, Pruhs, Ashrafi, & Post, 1983). In addition, practitioners often combine multiple classes of drugs (usually up to three—called a "triple cocktail" or "triple regimen") to get a synergistic effect and achieve optimal sedative effect, while minimizing adverse effects. If doses of each drug are not carefully calculated and responsibly used, overdoses may occur resulting in adverse reactions including death.

News in recent years has shone a spotlight on deaths in pediatric dentistry due to sedation, particularly with those that involved the drug chloral hydrate. Manufacturing of chloral hydrate has decreased in the US and several residency programs have stopped teaching sedation with the drug (Nelson & Xu, 2015). However, the number of anecdotal reports exceeds evidence-based conclusions on this topic. In this retrospective study, the safety and efficacy of a chloral hydrate containing triple cocktail drug regimen (chloral hydrate + meperidine + hydroxyzine) will be compared to a very common alternative (midazolam + meperidine + hydroxyzine).

2. BACKGROUND AND SIGNIFICANCE

2.1 Pediatric Oral Conscious Sedation

When a child is uncooperative for dental work in the chair, the pediatric dentist has several options to complete the child’s treatment. The first attempt is behavior guidance using tools such as tell-show-do, positive reinforcement, distraction, and hypnosis. Minimal sedation with inhaled nitrous oxide can also be used as an adjunct on
children who are anxious or for a long appointment. Nitrous oxide has an excellent track record when used according to guidelines (AAPD Guidelines, 2011). If these techniques are insufficient, the next tool in a pediatric dentist's arsenal is sedation, in which medications can be administered orally, intramuscularly, sublingually or intravenously. Sedation is defined by the AAPD guidelines as a "minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond to physical stimulation or verbal command and that is produced by a pharmacological or non-pharmacological method or a combination thereof" (AAPD Guidelines, 2011).

The oral route for sedation is most popular in pediatric dentistry (Nelson & Xu, 2015) — a child is given liquid or tablet medications orally and when the drug(s) start taking effect, the procedure is completed within the drugs' working time. The benefits of sedation include: better cooperation, completion of more dental work, possible amnesia, protection of the child's developing psyche, and relative inexpensiveness compared to general anesthesia (Nathan, 2015) (AAPD Guidelines, 2011). Since not every human has the same physiology and medications given orally cannot be titrated to effect, the medications may not have the same effect (Harbuz, Diana, & Michael, 2016). Thus, there is a chance of failure (inadequate sedation) for some children. For these cases, the remaining options are treatment with IV sedation or general anesthesia, both of which can be very expensive options for the parents. It should be noted that treatment with the patient placed in restraint such as a papoose board (without any sedation medications given) is falling out of favor due to changing parenting styles as well as changing training of pediatric dentists (Eaton, McTigue, Fields Jr, & Beck, 2005).
There is a spectrum of sedation that might result based on the dosage and number of medications given to the child. The spectrum covers three intended levels of sedation that are described in the AAPD Guidelines: 1) minimum 2) moderate and 3) deep. In intended minimal and moderate sedation, patients are expected to have a mild or moderate impairment, respectively, of cognitive function, are able to arouse and interact easily, and ventilation and cardiovascular function is maintained. In deep sedation, however, patients may not arouse even with a painful stimulus and intervention may be required to maintain their ventilation and cardiovascular function. In these cases, an anesthesiologist must be present to be able to control the depth of sedation and be ready to intubate the child should it be necessary. It is recommended by AAPD guidelines that oral sedation must be kept at minimum or moderate, since it is likely that some children may go one state higher than what is intended.

Administration of more potent medications and higher dosages leads to deeper levels of sedation (Nelson & Xu, 2015). Based on UCSF sedation guideline, minimum sedation is usually accomplished by one sedative drug (kept within the recommended dosage) and can be combined with 50% N2O and 50% oxygen. Moderate sedation is usually accomplished by using up to three drugs synergistically. In these triple cocktails sedations, dosages are kept well below maximum recommended limits to avoid getting the patient too deep sedation where respiratory and cardiovascular function may be compromised. For example, if one medication is "maxed out", the other two must be kept well below the maximum limit. It must be noted that local anesthesia and nitrous oxide/oxygen are two other medications also routinely utilized during oral sedations; thus, a triple cocktail sedation utilizes five medications in total.
2.2 Guidelines for Sedation (AAPD Guidelines)

2.2.1 Patient selection

It is vital to select a patient that is generally healthy such as ASA I or II. AAPD guidelines recommend against sedation a patient who is ASA III and above. Other medical contraindications to oral sedation are a patient with large tonsils (Brodksy score of 3 or 4), patient with sleep apnea that may easily obstruct, uncontrolled asthma, a patient that may need to be sedated multiple times to complete the extent of treatment, a patient that may have low baseline oxygen saturation due to cyanotic heart disease or certain syndromes (AAPD Guidelines, 2011).

2.2.2 NPO status

Patients are required to be "nil per os" (NPO) ie, withholding of oral foods and fluid at least 6 hours prior to most sedation appointment. The rationale is that there is a chance of aspiration should the child vomit and aspirate gastric contents during the appointment due to a depressed coughing reflex when sedated (AAPD Guidelines, 2011).

2.2.3 Personnel required

AAPD guidelines recommend the presence of, at the minimum, a dentist certified in pediatric life support, a staff member that acts as a monitor for vital signs during the sedation, and an assistant.

2.2.4 Monitoring for sedation

Because the patient's ventilation and cardiovascular function may be impaired after being medicated, it is important to have equipment to monitor vital signs during the sedation appointment, and have rescue medications ready to use if the situation demands. The AAPD guidelines recommend the following monitors for moderate
sedations: pulse oximeter to measure oxygen saturation and pulse, blood pressure cuff, and precordial stethoscope to hear breathing sounds and detect obstruction of the airway. These three monitors are routinely used at UCSF for triple cocktail sedations. The use of passive restraint such as papoose board is acceptable during sedations. It is important to distinguish false desaturations (ex. a combative patient kicks off the pulse oximeter) from true desaturations (Wilson, 1990). Capnography and EKG are not required unless a deep sedation is intended. Rescue medications that must be present include reversals for sedation medications, epinephrine in case of allergic reactions, positive pressure bag mask in case of desaturation, and oral (LMA) and nasal airways. An endotracheal tube and laryngoscope may not be needed unless a deep sedation is being conducted (AAPD Guidelines, 2011).

2.2.5 Delivering of medications

Oral sedation medications are delivered usually in a cup for the child to drink. If the child does not cooperate, the medications may be syringed into the mouth slowly. There is a chance for the child to spit out or vomit the medications either way. AAPD guidelines do not condone estimating the amount lost and re-administering medication since there is no accurate way of knowing how many milligrams were lost. It is also not recommended to attempt to titrate medications by estimating how sedated a child is as this can easily lead to overdosing. Guidelines strongly advocate against prescribing medications to be administered at home since misreading by pharmacist or parents can lead to over-dosage (AAPD Guidelines, 2011).
2.2.6 Immobilization

Immobilization devices such as papoose boards maybe used in sedation to restrict the child's movement but they must not cause airway obstruction or chest restriction (AAPD Guidelines, 2011).

2.2.7 Emergency

In case of failure of ventilatory or cardiovascular support, the dentist or staff member must administer the appropriate reversal agents, perform basic life support, and activate EMS (AAPD Guidelines, 2011).

2.3 Oral Sedation Medications Currently Used

There are a limited number of drug regimens currently used by pediatric dentists. A survey by Houpt 2000 showed that most pediatric dentists used drugs from the following classes: antihistamine (eg. hydroxyzine, promethazine), benzodiazepines (e.g. diazepam, midazolam, triazolam), opiates (eg. meperidine, morphine), and non-barbituate sedative-hypnotics (eg. chloral hydrate) (Houpt, 2002). At the pediatric dental clinic at the University of California, San Francisco (UCSF) where this study was conducted, the two most common triple cocktail regimens are midazolam, meperidine, hydroxyzine (Mid/M/H) and chloral hydrate, meperidine, hydroxyzine (CH/M/H). When used in combination, the dosages of these drugs are often lowered far below the maximum recommended dosage (MRD) values to ensure a good safety profile.

2.4 Characteristics of various classes of oral sedation medications

Antihistamines act on receptors in mast cells to reduce histamine release and cross the blood brain barrier and act on the tubermammillary nucleus of the brain to
cause drowsiness (Loew, 1947). Desirable characteristic of antihistamines include pleasant taste, bronchodilation, antiemesis, analgesia (Malamed, 1994).

Hydroxyzine is the antihistamine used in UCSF sedations. Its effects can be seen within 15-30 minutes and a duration of action of 2 to 4 hours. It is metabolized by the liver and has a half-life of 3 hours in adults (Simons, Simons, & Frith, 1984). The dosages used in the majority of studies is either 1-2 mg/kg or 1-4 mg/kg, with a max of 50 or 75 mg (Hasty, Vann, Dilley, & Anderson, 1991) (Shapira, 1992) (Needleman, 1995). The recommended dosage at UCSF Pediatric Dental Residency is 1-2 mg/kg with a max of 50 mg.

Benzodiazepines enhance the action of the neurotransmitter GABA at the GABA receptor in the limbic system causing sedation, sleepiness, anxiolysis, and muscle relaxation. Desirable characteristics of benzodiazepines include: high therapeutic index leading to a high safety profile and decreased likelihood of seizures, presence of a reversal agent, and possible anterograde amnesia (Page, Michael, Sutter, Walker, & Hoffman, 2002). Anterograde amnesia is useful in protecting the child's developing psyche from a stressful dental appointment. Undesirable characteristics include: displeasing taste and occasional paradoxical reactions such as disinhibition leading to agitation and panic (Saïas & Gallarda, 2008).

Midazolam is the benzodiazepine used at UCSF for triple cocktail sedations. Its effect of can be seen within 5-10 minutes after ingestion, with peak effect at 15 minutes. The duration of action is 30 min. It is metabolized by the liver. The dosages most frequently used in studies are 0.3-1 mg/kg with a max dose of 15 or 20 mg (Webb & Moore, 2002). At UCSF, the recommended dosage is 0.3- 0.75 mg/kg with a max dose
of 20 mg. The reversal for benzodiazepines in cases of overdose is flumazenil, which is a GABA receptor antagonist. It can be administered IV or sublingual, onset of action is rapid: within 1-2 minutes, and the recommended dosage is 0.01 mg/kg which can be repeated every minute if no effect until maximum of 0.05 mg/kg or 1 mg is reached, whichever is lower. Since benzodiazepines have longer half-lives than that of flumazenil, repeat dosages of the reversal may be required (Whitwam & Amrein, 1995) to prevent relapse of undesirable deep level of sedation.

Opiates act on the μ opioid receptors cerebrum to cause endorphin release, which can raise the pain threshold, sedation, and euphoria. The side effects of opioids include constipation, nausea, respiratory depression (when it acts on the medulla), lowering the seizure threshold, and histamine release, which can cause itching (Freye, 2008). Thus, an antihistamine such a hydroxyzine is often used in conjunction with the opioid to potentiate the CNS depression but to decrease the potential for nausea and itching. A benzodiazepine such as midazolam may also be used in combination to reduce the chance of seizures.

Meperidine is the opiate currently used at UCSF. Meperidine's effects can be seen in 30 minutes after ingestion. It has a duration of 2-4 hours. It is metabolized by the liver. The dosages most often used in studies are 1-2 mg/kg with a max dosage of up to 60 mg (Webb & Moore, 2002). The recommended dosage at UCSF is 1-2 mg/kg with maximum dose of 50 mg. The reversal for opioids is naloxone, which is a competitive antagonist for the μ receptors. It works within 2 minutes when given IV and 5 minutes when given IM. It lasts 30 minutes to 1hr, which means multiple doses may
be required, since the duration of action of most opioids exceeds that of naloxone (Freye, 2008).

Chloral hydrate is a unique drug that is in its own category of sedative-hypnotics. It is metabolized to trichloroethanol, which acts on GABA receptors (similar to benzodiazepines and barbiturates) to cause drowsiness. Side effects include gastric irritability with high doses leading to nausea, decreased myocardial contractility, and arrhythmogenic potential (Webb & Moore, 2002). Its onset is 30-60 min (Hobbs, Rall, & Verdoorn, 1996) (Webb & Moore, 2002), with peak effect at 2-5 hours, and it has a half-life of 7-10 hours in adults and more in children (Buck, 2005). Dosage used in most literature ranged from 25-75mg/kg with max dosage of 1-2g (Duncan, Pruhs, Ashrafi, & Post, 1983) (Webb & Moore, 2002). At UCSF, 50 mg/kg or 1000 mg is the maximum recommended dosage. Undesirable characteristics of chloral hydrate include unpleasant taste, gastric irritability, prolonged half-life (lethargy after sedation may last up to a full day, leading to chances of re-sedation), narrow therapeutic index, unpredictability of onset and duration, lack of reversal agent, ventricular arrhythmia, and paradoxical excitement in 6%-18% of cases in high doses (Pershad, Palmisano, & Nichols, 1999) (Nordt, 2014) (Lipshitz, Marino, & Sanders, 1993) (Zahedi, Grant, & Wong, 1999) (Bowyer & Glasser, 1980). Chloral hydrate is recommended to be used in children 2-4 years old (Webb & Moore, 2002). With older ages, there is higher chance of sedation failure (Rumm, Takao, & Fox, 1990) (Malviya, Voepel-Lewis, & Prochaska, 2000).
Table 1: Characteristics of Sedation Medications Used at UCSF for Triple Regimens

<table>
<thead>
<tr>
<th>effect</th>
<th>Midazolam</th>
<th>Meperidine</th>
<th>Hydroxyzine</th>
<th>Chloral Hydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>effect</td>
<td>CNS depressant</td>
<td>CNS depressant</td>
<td>CNS depression</td>
<td>CNS depression</td>
</tr>
<tr>
<td>antianxiety</td>
<td></td>
<td>analgesic</td>
<td>analgesic</td>
<td></td>
</tr>
<tr>
<td>side effects</td>
<td>- paradoxical</td>
<td>- resp. depression</td>
<td>+ anti histamine</td>
<td>- emesis (GI irritant)</td>
</tr>
<tr>
<td>excitement</td>
<td>+ amnesia</td>
<td>histamine release</td>
<td>+ anti emesis</td>
<td>+ arrhythmias at high</td>
</tr>
<tr>
<td>+ anticonvulsant</td>
<td>- resp. depression</td>
<td>itching etc</td>
<td>+ bronchodilation</td>
<td>doses</td>
</tr>
<tr>
<td>+ muscle relaxant</td>
<td>threshold</td>
<td>lower seizure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ antispasmodic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dosage (max)</td>
<td>.3-.75mg/kg (15-20 mg)</td>
<td>1-2 mg/kg (50 mg)</td>
<td>1-2 mg/kg (75mg)</td>
<td>25-50 mg/kg (1000 mg)</td>
</tr>
<tr>
<td>onset</td>
<td>5-10 min</td>
<td>30 min</td>
<td>15-30 min</td>
<td>30-60 min</td>
</tr>
<tr>
<td>duration</td>
<td>30 min</td>
<td>2-4 hrs</td>
<td>2-4 hrs</td>
<td>5-8 hrs</td>
</tr>
<tr>
<td>reversal</td>
<td>flumazenil</td>
<td>naloxone</td>
<td>-</td>
<td>none</td>
</tr>
</tbody>
</table>

(Websites: Webb & Moore, 2002; Hobbs, Rall, & Verdoorn, 1996; Malamed, 1994)

2.5 Debate Regarding Chloral Hydrate

Although it was a popular drug of choice for sedation in the past, use of chloral hydrate has fallen out of favor in recent times. This could be due to several deaths on the news involving the drug, the lack of reversal agent, and the advent of newer drugs that have come into the market (such as benzodiazepines which have a high therapeutic index). Unfortunately, with the exception of Texas, there is no national or state law mandating dentists to report dosage of medications used in deaths related to sedation. The information regarding the adverse event and doses of medication used may be released only at the discretion of the lawyer that has taken up the case for the dentist. Thus, in most cases, the only data available is that gathered by news reporters, FDA adverse drug reporting system, or autopsy reports.

Table 2 is a summary of recent adverse events involving chloral hydrate in pediatric dentistry gained from news reports as well as available literature (Nordt, 2014) (Nelson & Xu, 2015), both of which often give an incomplete picture. It should be noted
that in nearly every case of adverse events, the AAPD guidelines for sedation had been violated or overdosing had occurred. In one case, re-dosing had occurred; in two cases, medications were administered at home; in another case, patient had a syndrome of dwarfism (low weight which could lead to easier overdosing); in five cases, overdosing had occurred. It is interesting to note that death had occurred with a 300 mg overdose of chloral hydrate whereas a patient recovered with 5000 mg overdose of the same. This unpredictability of adverse outcome is also another reason the medication has fallen out of favor (Pershad, Palmisano, & Nichols, 1999). In the two cases where an acceptable dose was given, no significant adverse events occurred, showing that chloral hydrate seems to be safe when used within the safety range and administered according to guidelines.

It is also important to note, that in most cases resulting in adverse events, chloral hydrate is not the only drug administered and AAPD oral conscious sedation guidelines have been violated. This means that the adverse event cannot be confidently attributed only to chloral hydrate. Cote (Cote, Karl, & Notterman, 2000) reviewed adverse events pulled from various sources and noted that of 20 patients that received chloral hydrate for either medical or dental procedures, 7 received only chloral hydrate, of which only 1 patient received a standard dose (60mg/kg) and still had an adverse event. The other 6 received an overdose or an unknown amount.

Chloral hydrate is a drug that is still not approved by the FDA for any medical indication but is still prescribed by clinicians as off label (Meadows, 2007). There are several medications used for pediatric population are not yet FDA approved because the approval process requires lengthy and complex clinical trials, which are involved 3
clinical trials: 2 of which must be conducted in the USA and at most 1 can be conducted abroad. Success rate of chloral hydrate has been shown to be 89-100% (Pershad, Palmisano, & Nichols, 1999), with higher success below age of four (Mace, Brown, Francis, & et-al, 2008) (Rumm, Takao, & Fox, 1990) (Malviya, Voepel-Lewis, & Prochaska, 2000). It is known to have a high safety factor with few side effects when used appropriately (Sim, 1975).

Chlortal hydrate was used by 62% of diplomates of AAPD in 1983 (Duncan, Pruhs, Ashrafi, & Post, 1983) but is now used by fewer pediatric dentists (Nelson & Xu, 2015). Residency programs that continue to use the medication include University of California, San Francisco (as of 2016), Columbus Children's Hospital at Ohio State University (as of 2000), and the University of Iowa College of Dentistry (as of 2005), and University of North Carolina at Chapel Hill (as of 2016).

Table 2: Adverse events involving chloral hydrate in pediatric dental sedation

<table>
<thead>
<tr>
<th>Date</th>
<th>Age/sex</th>
<th>Adverse Event</th>
<th>Violation of guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>8 F</td>
<td>death</td>
<td>1300 mg CH (MRD: 1000)</td>
</tr>
<tr>
<td>? *</td>
<td>2 M</td>
<td>seizures, hospitalized, recovered</td>
<td>5.8 mg/kg hydroxyzine (MRD: 4 mg/kg)</td>
</tr>
<tr>
<td>? *</td>
<td>4</td>
<td>unarousable, hospitalized, recovered</td>
<td>4 carpules 2% lidocaine 1:100k, 2x 500mg CH</td>
</tr>
<tr>
<td>2013</td>
<td>3 F</td>
<td>death</td>
<td>40% above MRD of CH+Mep+Hyd</td>
</tr>
<tr>
<td>? *</td>
<td>8 M</td>
<td>hypoxic brain damage</td>
<td>1700 mg CH, 4.4 mg/kg Hyd</td>
</tr>
<tr>
<td>? *</td>
<td>4 F</td>
<td>death after discharge</td>
<td>CH taken at home, suspect resedation</td>
</tr>
<tr>
<td>? *</td>
<td>3 M</td>
<td>ventricular instability, hospitalized</td>
<td>6000 mg administered at home (mom couldn't read written directions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treated, recovered</td>
<td></td>
</tr>
<tr>
<td>? *</td>
<td>2 M</td>
<td>death</td>
<td>dosage not reported. Russel-Silver syndrome.</td>
</tr>
<tr>
<td>? *</td>
<td>5 M</td>
<td>insignificant (slept)</td>
<td>none (1000 mg CH)</td>
</tr>
<tr>
<td>? *</td>
<td>3</td>
<td>insignificant (bumped head)</td>
<td>none (1000 mg CH)</td>
</tr>
</tbody>
</table>

A literature review shows there is conflicting evidence on the safety and effectiveness of chloral hydrate in pediatric dental oral sedation. Effectiveness of sedation is often characterized by behavior control and cooperation of the patient as well as the amount of work completed. Layangool (Layangool & et-al, 2008) and Dallman (Dallman, MA, & Biskie, 2001) have concluded that midazolam is as effective, if not more. Hare (Hare, 2012) and D'Agostino (D'Agostino & Terndrup, 2000) state that chloral hydrate resulted in better sedation than other medications. Leelataweedwud (Leelataweedwud & Vann, 2011) looked at 111 children aged 2-4 years that were given a regimen of chloral hydrate + meperidine+ hydroxyzine and concluded that the success rate was 72%.

Multiple studies unfairly compared a single agent regimen with a double agent chloral hydrate regimen (Houpt, 2002) (Dallman, MA, & Biskie, 2001), single with double (Hasty, Vann, Dilley, & Anderson, 1991) (Wilson, 1990), or single with triple (Chowdury & Vargas, 2005) (Wilson, 1990) and concluded that the double agent regimen were more successful than single, and triple were more successful than single or double, as one would expect. Comparing a single drug to multiple drugs is inappropriate since the success of the multiple drug regimen can be attributed to 1) the sheer number of drugs involved or 2) the dosage rather than the biochemistry of the drug itself. Badalaty (Badalaty & et-al., 1990) compared single agent chloral hydrate with single agent (but double dose) of diazepam and concluded that chloral hydrate was still more effective.

There are also limited studies on the safety of chloral hydrate used in sedation. Safety of oral sedation is often characterized by the number of adverse events that occur during or after the sedation such as: desaturation of 3-4%, vomiting, over-
sedation, need for airway intervention, brain damage, or death (Cote 2006). Some articles state (Sim, 1975) it has a high safety profile whereas others (Layangool & et-al, 2008) (Dallman, MA, & Biskie, 2001) state that it is no longer needed to be used, since there are newer and safer medications on the market. Few studies exist that actually calculated safety by noting the number of adverse events that occur with chloral hydrate used alone or in combination with other medications. One study (Leelataweedwud & Vann, 2011) showed that out of 111 visits 6 (3%) resulted in adverse events such as apnea, over-sedation, desaturation, and vomiting.

Only one study proves to be valid in comparing the safety and effectiveness of chloral hydrate. Sheroan (Sheroan & et-al., 2006) compared two triple cocktail regimens with controlled dosing: patients were given either a cocktail of 50 mg/kg chloral hydrate + 25 mg hydroxyzine + 1.5mg/kg meperidine or 1 mg/kg midazolam + 25 mg hydroxyzine + 1 mg/kg meperidine. They found no significant differences in behavior or physiological parameters. The chloral hydrate regimen resulted in two patients that had 10 separate desaturation events, but the regimen was also deemed to be slightly more successful. The authors rationalized the desaturations to the operator having unknowingly put pressure on mandible forcing the head to tilt down, obstructing the flow of oxygen. It must be noted that although this is the most controlled study of the ones reviewed, there is still one confounding factor: the dosage of meperidine was not equal in both regimens. The authors did not state their reasons for not maintaining the same dosage in this prospective study.
2.6 Aims, Hypothesis, Significance

2.6.1 Aims

There were two aims of this study: 1) evaluate the safety and 2) evaluate the effectiveness of two triple cocktail regimens in pediatric dental oral sedation: chloral hydrate + meperidine + hydroxyzine versus midazolam + meperidine + hydroxyzine. Safety is defined as desaturation of 3-4%, vomiting, and/or over-sedation. Effectiveness is defined as the patient's behavior and cooperation level during treatment and the amount of work completed.

2.6.2 Null Hypothesis

The null hypothesis of the study was that there would be no significant difference in the safety or efficacy of the two triple cocktail regimens.

2.6.3 Significance

There is a recent trend of removing the use of chloral hydrate from private clinics as well as residencies due to adverse events including death. However, most adverse events resulted when there was a lack of adherence to guidelines and protocol. There is a lack of valid research on chloral hydrate's use in pediatric dentistry, and this study aims to reflect on the safety and efficacy of the drug when guidelines are followed.

3. METHODS AND MATERIALS

This study was approved by the Committee on Human Research at the University of California, San Francisco (IRB Number 15-17748). This was a retrospective study of two triple-cocktail oral sedation regimens (chloral hydrate + meperidine + hydroxyzine vs. midazolam, meperidine + hydroxyzine) based on a
sample of charts that met inclusion criteria from Oral Conscious Sedation Clinic at UCSF Pediatric Dentistry.

3.1 Standard Operating Procedures of Moderate Oral Conscious Sedation

All sedations done at UCSF Pediatric Dentistry follow a standardized sedation protocol. A patient may be referred to sedation if an operative appointment with nitrous fails or due to the extent of work that the patient may not be able to tolerate. The child is given a "pre-sedation behavior score" of 1, 2, or 3 on the “Pre-Sedation Form”. A score of 1 means the patient is mostly cooperative but may need anxiolysis. A score of 2 means the patient will not cooperate for radiographs or is moderately uncooperative. A score of 3 means the child is defiant or uncontrollable. The child's Mallampati and Brodsky score are checked by the provider. A child with Mallampati or Brodksy of 4 usually is not sedated.

Parents of the child to be sedated are given a discussion of risks, benefits, and alternatives to oral sedation. Once parents have consented, a history and physical form is given to be completed by the child's physician. An appointment is given only when the pediatrician has signed that there are no contraindications for oral sedation. When the form is received, a "pre-sedation" visit is scheduled. The parents are explained the following requirements: patient must be NPO at least 6 hours before the sedation appointment, two adults need to accompany the child should the mode of transportation be driving (so one adult can ensure the child is not obstructing his/her breath if he/she were to fall asleep on the way home), patient must wear comfortable clothing, and no nail polish or clothing covering fingers or toes so pulse oximeter can read well. The parents are also informed of the drug regimen that will most likely be used.
Residents do a "write-up" that will be emailed to the sedation attending that lists medical history, patient's behavior at previous visits, the treatment plan, and suggests a drug regimen including dosages of all drugs that will be given as well as reversal agents should they become necessary. The attending receives this write-up at least one week in advance of the appointment and will suggest the necessary changes.

On the day of the sedation, the operator confirms that the patient has been NPO for at least 6 hours, that patient is not currently ill or has fever (provider auscultates lungs to confirm no wheezing or obstructive breathing), baseline vitals are taken if patient cooperates (blood pressure, pulse, breathing rate, oxygen saturation), current weight is obtained, and the Mallampati and Brodsky scores are confirmed. All necessary rescue medications, rescue equipment, and monitors are laid out in the operating room with easy access. Suction and oxygen delivery systems are checked to be functioning.

The medications are drawn and mixed with the presence of the attending and given to the child in a cup. If the child refuses to drink the medications, they may be syringed in a knee-to-knee manner. It is noted whether the child spat out and how many milliliters of the concoction were lost. The child is allowed to sit with parents until the medications take effect. The wait time may vary based on the faculty attending as well as the child's physiology but usually is in the range recommended by literature. Then, the child is moved to the operating room and parents are usually asked to wait in waiting area. The child is placed on a papoose board and monitors are attached. The precordial stethoscope is placed on the sternal notch. The operator (via earphones) and the monitor (via Bluetooth headset) listen to breathing sounds. The pulse oximeter is placed on the big toe of one foot while the blood pressure cuff is placed on the other
leg. The papoose restraints are typically used if the child shows indications of moving. Nitrous oxide, through a nasal mask, is titrated to effect. Local anesthesia is administered, and the operative work is commenced. Monitoring of vital signs is done every five minutes throughout the procedure as long as the child does not kick them off. After completion, 100% oxygen is given for five minutes and child is taken back to parents. The parents are given post-operative instructions verbally and in written format. The child is discharged when vitals have returned to 20% within baseline and child is awake and oriented. A follow-up phone call may or may not have been made by the operator the same evening.

The documentation of the sedation is done on a form called the Sedation Log (see Appendix 8.1 "Sedation Log"). This includes patient identifiers; weight; relevant medical history; Mallampati and Brodsky scores; types of, dosages of, as well as times at which every single medications were given; patient's vital signs every 5 minutes; time patient was brought in and brought out of the operating room; treatment planned and treatment completed; patient behavior before, during, and after treatment; and sedation depth throughout the treatment. This information, except for log of vital signs, is also typed in the clinical note in the electronic health record, AxiUm ©. If a follow-up phone call was made, it is typically noted in the clinical note as well.

3.2 Subjects, Study design, Data Collection
This is a retrospective study. All 1,016 sedation logs that existed from 1/1/2003-6/3/2015 at UCSF Pediatric Sedation Clinic were chronologically screened. All data was collected from one or more of the following: sedation log form, pre-sedation form, or clinical note. The data was entered in REDCap (Research Electronic Data Capture)
Database Software on campus by a resident (researcher of this project), a dentist and pre-doctoral student interested in this research project. All information pertaining to this study was saved in the UCSF secure server. When data collection was complete, it was exported as a Microsoft Excel sheet for data analysis with SAS software. Patient identifiers in this data sheet included dental chart numbers and date of birth.

The inclusion criteria included the following:

- Patient seen at UCSF Pediatric Dental Sedation Clinic
- Patient was given a triple cocktail of either chloral hydrate, meperidine, hydroxyzine (CH/M/H) or midazolam, meperidine, hydroxyzine (Mid/M/H)
- Both a hard copy of the sedation log and AxiUm clinical notes were present (this allows cross checking of data to ensure accuracy of records since photocopies of the sedation log may be difficult to read)
- Chart has the mandatory data listed below:
  - Chart number
  - Date of service
  - Date of birth (to calculate age)
  - Weight in kilograms at time of sedation
  - Types and amounts of all drugs used- sedation drugs, nitrous oxide, local anesthesia
  - Behavior during sedation (converted into a modified Frankl scale- see table 4)
  - Adverse reactions:
    - desaturations of more than 4%
- vomiting
- over-sedation
  - stated as being over-sedated and/or
  - a sedation depth score of 4 or 5 noted on Sedation Log (see table 3) and/or
  - reversal was given

The exclusion criteria included:

- Duplicate sedation logs
- Missing patient identifiers on the sedation logs

Data that was also recorded if present was:

- Pre-sedation behavior score
- Sedation depth from sedation log (see table 3)

### Table 3: Sedation Depth Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation depth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>anxious</td>
</tr>
<tr>
<td>2</td>
<td>awake/oriented</td>
</tr>
<tr>
<td>3</td>
<td>sleepy/easily arousable</td>
</tr>
<tr>
<td>4</td>
<td>difficult to arouse</td>
</tr>
<tr>
<td>5</td>
<td>not arousable</td>
</tr>
</tbody>
</table>

All data was objective except for descriptions of patient behaviors, which were not standardized amongst residents. The descriptions on the Sedation Log or clinical note included a spectrum of all possible behaviors: sleeping, being quiet, crying, moving, kicking, screaming, being combative, struggling, and being defiant. It is also noted if the sedation was aborted due to the poor cooperation. All of this subjective data was converted to a modified Frankl behavior scale to include all the information provided by the operators (see table 4).
Table 4: Behavior Scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sleeping</td>
</tr>
<tr>
<td>2</td>
<td>Quiet</td>
</tr>
<tr>
<td>3</td>
<td>moving/crying</td>
</tr>
<tr>
<td>4</td>
<td>Struggling/defiant but treatment completed</td>
</tr>
<tr>
<td>5</td>
<td>Struggling/defiant and treatment aborted</td>
</tr>
</tbody>
</table>

3.3 Data Analysis

For aim 1 (safety), the number and type of adverse events were summarized as frequencies and percentages by group and compared with Fisher’s exact test or chi-squared test for significant difference between groups.

For aim 2 (efficacy), the number and percentage of occurrences of the five different behaviors were summarized by group and compared by chi-squared test or Fisher’s exact test. The mean, median and standard deviation of the behavior score were also computed by group and compared with Wilcoxon’s rank sum test.

4. RESULTS

Of the 1016 charts that were screened, 295 met inclusion criteria (see Figure 1). Charts from 2003-2010, which were 328 in total, were excluded since there were no electronic clinical notes (the EHR AxiUm was implemented on 7/21/2010 at UCSF). Of the 295 charts, 141 were CH/M/H and 154 were Mid/M/H triple cocktails.
4.1 Age

The age range of sedations was from 2 to 11 for CH/M/H and 2 to 14 Mid/M/H regimen. The average age of the patient for the Mid/M/H regimen was 4.37±2.93 and for CH/M/H was 4.01±2.61 (see Figure 2). There was no significant difference in age between the two groups (Unpaired T test p= 0.43).

4.2 Safety: Adverse Events

Of the 295 cases, adverse events occurred in 27 (9.1% of all cases). Eleven (7.8% of total adverse reactions) of these were CH/M/H regimens and 16 (10% of total...
adverse reactions) were Mid/M/H regimens (see Table 5). A Fischer’s exact test resulted in \( p = 0.2610 \). Being greater than 0.05, the null hypothesis was rejected. Thus there was no statistical difference in adverse reactions between the two regimens.

**Table 5: Adverse Events between two triple-regiments**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Mid/M/H</th>
<th>CH/M/H</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Desaturation</td>
<td>6</td>
<td>4.26%</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>6.38%</td>
<td>6</td>
</tr>
<tr>
<td>Over-sedation</td>
<td>1</td>
<td>0.71%</td>
<td>3</td>
</tr>
<tr>
<td>None</td>
<td>125</td>
<td>88.65%</td>
<td>143</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>141</td>
<td>100%</td>
<td>154</td>
</tr>
</tbody>
</table>

**Figure 3: Graphical Representation of Adverse Events**

Figure 3: 11% of Mid/M/H regimens resulted in adverse reactions vs 9% in CH/M/H regimens. There was no significant difference between the two regimens (Fisher’s exact test \( p = 0.2610 \)).

**4.3 Efficacy: Behavior Outcomes and Success of Treatment**

The number of cases resulting in each behavior score from 1-5 are tabulated in Table 6 and graphically represented in Figure 4. From the 295 cases, the average behavior score was 2.88 (median = 3) for Mid/M/H which was closer to “crying/moving”
whereas it was 2.03 (median =2) for CH/M/H, which was closer to "quiet". Both chi$^2$ analysis and thus, the CH/M/H regimen showed to be statistically resulting in better behavior than the Mid/M/H regimen.

Table 6: Behavior Outcomes

<table>
<thead>
<tr>
<th>Behavior score</th>
<th>Mid/M/H</th>
<th>CH/M/H</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>1: sleeping</td>
<td>14</td>
<td>9.1%</td>
<td>66</td>
</tr>
<tr>
<td>2: quiet</td>
<td>38</td>
<td>24.7%</td>
<td>29</td>
</tr>
<tr>
<td>3: crying/moving</td>
<td>66</td>
<td>42.9%</td>
<td>30</td>
</tr>
<tr>
<td>4: struggling, completed</td>
<td>24</td>
<td>15.6%</td>
<td>8</td>
</tr>
<tr>
<td>5: struggling, aborted</td>
<td>12</td>
<td>7.8%</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>100%</td>
<td>141</td>
</tr>
</tbody>
</table>

Figure 4: Graphical representation of efficacy

Figure 4: Average behavior score was 2.88 (median=3) for Mid/M/H regimen whereas it was 2.03 (median=2) for CH/M/H. CH/M/H regimen showed to be statistically resulting in better behavior than the Mid/M/H regimen (Chi$^2$ test p<0.0001).

To look at the overall success (defined as completion of treatment) or failure (defined as abortion of treatment), data were combined and tabulated in Table 7 and graphically represented in Figure 5. Slightly more CH/M/H regimens were successful
than Mid/M/H regimens. However, a chi-squared test (P= 0.4697) showed that the difference was insignificant.

Table 7: Success of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Mid/M/H</th>
<th>CH/M/H</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>completed</td>
<td>142</td>
<td>92.2%</td>
<td>133</td>
</tr>
<tr>
<td>aborted</td>
<td>12</td>
<td>7.8%</td>
<td>8</td>
</tr>
<tr>
<td>total</td>
<td>154</td>
<td>100%</td>
<td>141</td>
</tr>
</tbody>
</table>

Figure 5: Success of treatment

Figure 5: 94% of CH/M/H regimens were successful vs 92% of Mid/M/H regimens. The difference was insignificant (Chi$^2$ test test P= 0.4697).

4.4 Age and Efficacy

To see if efficacy of CH/M/H over Mid/M/H changed with age, odds ratios with 95% Wald confidence limits were calculated at each age from 2-13 (see Table 8 and Figure 6). Bigger OR’s were found at younger ages, meaning that there was more
likelihood of more cooperative behavior with CH/M/H as opposed to Mid/M/H at younger ages. This difference becomes statistically insignificant at age 9 (at $\alpha= 0.5$) which is the smallest age where the confidence interval contains the value 1.0 ($OR = 2.315$, 95% CI: 0.729, 7.349). After this age, the sample size was too small to make an accurate statement about significance.

**Table 8: Odds Ratios at Each Age Group**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Estimate</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP CH vs Mid at AGE=2</td>
<td>6.926</td>
<td>3.556</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=3</td>
<td>5.923</td>
<td>3.508</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=4</td>
<td>5.064</td>
<td>3.226</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=5</td>
<td>4.330</td>
<td>2.677</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=6</td>
<td>3.703</td>
<td>2.035</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=7</td>
<td>3.166</td>
<td>1.474</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=8</td>
<td>2.707</td>
<td>1.043</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=9</td>
<td>2.315</td>
<td>0.729</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=10</td>
<td>1.979</td>
<td>0.506</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=11</td>
<td>1.693</td>
<td>0.350</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=12</td>
<td>1.447</td>
<td>0.242</td>
</tr>
<tr>
<td>GROUP CH vs Mid at AGE=13</td>
<td>1.237</td>
<td>0.167</td>
</tr>
</tbody>
</table>
Figure 6: Younger age groups had higher odds of showing more cooperative behavior with CH/M/H as opposed to Mid/M/H. After the age of 9, the difference in behavior between the two regimens becomes insignificant at $\alpha=0.5$ since the confidence interval contains the value 1.0 at ages 9-13.

4.5 Pre-sedation Behaviors and Efficacy

Pre-sedation behavior scores were also compared to sedation behavior scores to rule out the effect of pre-sedation behavior on the results of either regimen. Out of the 295 charts, 109 had a recording of pre-sedation behavior scores (see Table 9 and Figure 7). Of the 109, 69 were Mid/M/H regimen and 40 charts were CH/M/H regimen. For the Mid/M/H regimen, if the pre-sedation behavior was a 1 (mostly cooperative to begin with), the mean sedation behavior score was a 2.8 and the median score was a 3 (crying/moving); if the pre-sedation behavior was 2 (patient did not cooperate easily to begin with), the mean was a 3.1 (median= 3); if the pre-sedation behavior was a 3 (patient was defiant to begin with), the mean was a 3.1 (median =2.5). For the CH/M/H regimen, the average sedation behavior score was a 2 (median =2) if the pre-sedation
behavior was 1; it was a 2.2 (median =2) if the pre-sedation behavior was a 2; it was a 2.6 (median 2) if the pre-sedation behavior was a 3. Having a pre-sedation score of 1 or 3 did not have a significant effect on the outcomes of the two regimens. However, having a pre-sedation score of 2 was significant (p=0.0155): CH/M/H regimen resulted in significantly better behavior when the child was classified as a “2” than the Mid/M/H regimen.

**Table 9: Pre-sedation Behavior Scores vs. Sedation Behavior Scores**

<table>
<thead>
<tr>
<th>Sedation behavior</th>
<th>Presedation behavior score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mid</td>
<td>CH</td>
<td>both</td>
<td>Mid</td>
<td>CH</td>
</tr>
<tr>
<td>1: sleeping</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>2: quiet</td>
<td>7</td>
<td>4</td>
<td>11</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>3: crying/moving</td>
<td>13</td>
<td>6</td>
<td>19</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>4: struggling, completed</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>5: struggling, aborted</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27</td>
<td>16</td>
<td>43</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td><strong>Average sed. score</strong></td>
<td>2.8</td>
<td>2.0</td>
<td>2.5</td>
<td>3.1</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Median sed. score</strong></td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
4.6 Operator Experience Effect on Safety

One confounding factor on safety of the regimens could be which year in residency the operator was in. It could be argued that 3rd year residents (final year of residency) would have more experience in rescue maneuvers and adverse reactions would therefore occur less often than when a 2nd year resident is the operator. To analyze this, the number of adverse reactions that occurred and the experience of the operator were tabulated in Table 9. Of 295 charts, 270 had records of whether the operator was a 2nd or 3rd year. And of the 27 adverse reactions that were recorded in total, 25 cases had records of whether the operator was a 2nd or 3rd year. Slightly more adverse reactions occurred when the operator was a 2nd year. However, this was not significant (Fisher’s exact test p=0.5339) (Table 10). It must be kept in mind that only 34 cases were done by 2nd year residents whereas 236 were done by 3rd years.
Table 10: Operator Experience and Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>2nd year</th>
<th>%</th>
<th>3rd year</th>
<th>%</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions</td>
<td>4</td>
<td>11.8%</td>
<td>21</td>
<td>8.9%</td>
<td>25</td>
</tr>
<tr>
<td>No adverse reactions</td>
<td>30</td>
<td>88.2%</td>
<td>215</td>
<td>91.1%</td>
<td>245</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>100%</td>
<td>236</td>
<td>100%</td>
<td>270</td>
</tr>
</tbody>
</table>

Fisher’s exact test p=0.5339

Of the 25 adverse reactions, 4 were when a 2nd year was the operator and the rest were when a 3rd year was the operator. Again, it is important to remember that only 34 cases were known to be completed by 2nd year residents, thus the chance of adverse reactions reduces accordingly compared to 3rd year resident cases. Of the 4 adverse reactions, all were vomiting. Of the 21 adverse events that occurred with 3rd years, the majority was also vomiting, followed by desaturation, and finally oversedation. Thus overall, vomiting was the most common adverse event regardless of the type of drugs used. There was no significant difference between operator experience and occurrence of adverse reactions (Fisher exact test p= 0.1833) (Table 11 and Figure 8).

Table 11: Operator Experience and Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>2nd year</th>
<th>%</th>
<th>3rd year</th>
<th>%</th>
<th>total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>desaturation</td>
<td>0</td>
<td>0%</td>
<td>8</td>
<td>38%</td>
<td>8</td>
<td>32%</td>
</tr>
<tr>
<td>vomiting</td>
<td>4</td>
<td>100%</td>
<td>9</td>
<td>42%</td>
<td>13</td>
<td>52%</td>
</tr>
<tr>
<td>oversedation</td>
<td>0</td>
<td>0%</td>
<td>4</td>
<td>19%</td>
<td>4</td>
<td>16%</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>100%</td>
<td>21</td>
<td>100%</td>
<td>25</td>
<td>100%</td>
</tr>
</tbody>
</table>
### 4.7 Operator Experience Effect on Efficacy

Similar to how operator experience may affect safety, it may also affect efficacy and success of the sedation. Third year residents can be expected to have more behavior management capabilities than 2nd year residents. To see if this is true, sedation scores were separated based on operator experience for each regimen in Table 12.

For the Mid/M/H regimen, both 2nd and 3rd years had crying/moving behavior the most. The graphs (Figure 9) for both types of residents align similarly showing there was no significant difference (Fisher exact test $p=0.7757$) of being a 2nd or 3rd year resident and the sedation outcome with the Mid/M/H regimen. Table 13 shows that 3rd year residents were slightly more successful overall in completing Mid/M/H regimens than 2nd years, but the result is not significant (Fisher exact test $p =0.6892$).
Table 12: Operator Experience and Behavior Outcomes with Mid/M/H Regimen

<table>
<thead>
<tr>
<th>Sedation depth scale</th>
<th>2nd year</th>
<th>%</th>
<th>3rd year</th>
<th>%</th>
<th>total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: sleeping</td>
<td>3</td>
<td>12%</td>
<td>9</td>
<td>7.7%</td>
<td>12</td>
<td>8.5%</td>
</tr>
<tr>
<td>2: quiet</td>
<td>4</td>
<td>16%</td>
<td>28</td>
<td>23.9%</td>
<td>32</td>
<td>22.5%</td>
</tr>
<tr>
<td>3: crying/moving</td>
<td>13</td>
<td>52%</td>
<td>52</td>
<td>44%</td>
<td>65</td>
<td>45.8%</td>
</tr>
<tr>
<td>4: struggling/defiant, treatment completed</td>
<td>3</td>
<td>12%</td>
<td>20</td>
<td>17%</td>
<td>23</td>
<td>16.2%</td>
</tr>
<tr>
<td>5: struggling/defiant, treatment aborted</td>
<td>2</td>
<td>8%</td>
<td>8</td>
<td>6.8%</td>
<td>10</td>
<td>7.0%</td>
</tr>
<tr>
<td>total</td>
<td>25</td>
<td>100%</td>
<td>117</td>
<td>100%</td>
<td>142</td>
<td>100%</td>
</tr>
</tbody>
</table>

Figure 9: In the Mid/M/H group, similar number of behavior outcomes resulted with both types of residents. There was no significant difference (Fisher exact test $p=0.7757$) of being a 2nd or 3rd year resident and the sedation outcome with the Mid/M/H regimen.
Table 13: Operator Experience and Success of Treatment for Mid/M/H Regimen

<table>
<thead>
<tr>
<th></th>
<th>2nd year</th>
<th>%</th>
<th>3rd year</th>
<th>%</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>completed</td>
<td>23</td>
<td>92%</td>
<td>109</td>
<td>93.2%</td>
<td>132</td>
</tr>
<tr>
<td>Aborted</td>
<td>2</td>
<td>8%</td>
<td>8</td>
<td>6.8%</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100%</td>
<td>117</td>
<td>100%</td>
<td>142</td>
</tr>
</tbody>
</table>

P=0.6892 Fisher’s exact test

As for the CH/M/H regimen, both 2nd and 3rd years had sleeping behavior the most (Table 14). The graphs (Figure 10) for both types of operators align similarly once again, showing there was no significant difference (Fisher exact test p = 0.9179) of being a 2nd or 3rd year resident and the sedation outcome with CH/M/H. Similar to the other regimen, 3rd year residents were slightly more successful in completing sedations with CH/M/H than 2nd years (see Table 15). Again, however, the difference was not significant (Fisher exact test p = 0.4515).

Table 14: Operator Experience and Sedation Depth Score with CH/M/H Regimen

<table>
<thead>
<tr>
<th>Sedation depth scale</th>
<th>2nd year</th>
<th>%</th>
<th>3rd year</th>
<th>%</th>
<th>total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: sleeping</td>
<td>4</td>
<td>44.4%</td>
<td>54</td>
<td>45.4%</td>
<td>58</td>
<td>45.3%</td>
</tr>
<tr>
<td>2: quiet</td>
<td>2</td>
<td>22.2%</td>
<td>25</td>
<td>21.0%</td>
<td>27</td>
<td>21.1%</td>
</tr>
<tr>
<td>3: crying/moving</td>
<td>2</td>
<td>22.2%</td>
<td>26</td>
<td>21.8%</td>
<td>28</td>
<td>21.9%</td>
</tr>
<tr>
<td>4: struggling, completed</td>
<td>0</td>
<td>0%</td>
<td>7</td>
<td>5.9%</td>
<td>7</td>
<td>5.5%</td>
</tr>
<tr>
<td>5: struggling, aborted</td>
<td>1</td>
<td>11.1%</td>
<td>7</td>
<td>5.9%</td>
<td>8</td>
<td>6.3%</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100%</td>
<td>119</td>
<td>100%</td>
<td>128</td>
<td>100%</td>
</tr>
</tbody>
</table>
Figure 10: Operator Experience and Sedation Depth Scale with CH/M/H Regimen

![Operator Experience and Sedation Depth Scale with CH/M/H Regimen](image)

Figure 10: In the CH/M/H group, similar number of behavior outcomes resulted with both types of residents. There was no significant difference (Fisher exact test $p = 0.9179$) of being a 2$^{nd}$ or 3$^{rd}$ year resident and the sedation outcome with the CH/M/H regimen.

Table 15: Operator experience and success of treatment for CH/M/H regimen

<table>
<thead>
<tr>
<th></th>
<th>2$^{nd}$ year</th>
<th>%</th>
<th>3$^{rd}$ year</th>
<th>%</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>completed</td>
<td>8</td>
<td>88.9%</td>
<td>112</td>
<td>94.1%</td>
<td>120</td>
</tr>
<tr>
<td>Aborted</td>
<td>1</td>
<td>11.1%</td>
<td>7</td>
<td>5.9%</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100%</td>
<td>119</td>
<td>100%</td>
<td>128</td>
</tr>
</tbody>
</table>

Fisher’s exact test $p=0.4515$

4.8 Cases Where Patients Were Given More than Maximum Dosage

Despite usual agreement of and adherence to the dosage levels described in Table 1 by the UCSF faculty attending sedations, there were several instances when patients were given more than the maximum recommended dose levels. In 3 Mid/M/H cases, more than the MRD of 20 mg of midazolam was administered, with highest dose being 50 mg. None of these three cases resulted in adverse events. In 12 cases, more
than MRD of 50 mg of meperidine was administered, with highest dosage being 75 mg. One case resulted in vomiting (60 mg used on a 7 year old) and one case resulted in over-sedation (60 mg used on a 8 year old with developmental delay). There were no cases were chloral hydrate or hydroxyzine was given beyond the MRD of 1000mg and 75 mg, respectively. No case had multiple drugs that went beyond the MRD.

4.9 Cases Where Medications Were Titrated

As described in the "Guidelines for Sedation" section of the introduction, oral medications are not meant to be titrated since it cannot be accurately known how much was absorbed by the child's gastrointestinal tract (first pass effect) (Harbuz 2016). Although some practitioners may find it convenient to assess the child's behavior after a first dose of medications and then add another dose if patient's behavior is not cooperative enough, such actions are condoned by UCSF Pediatric Dental Sedation Clinic. There was only one case of the 295 charts, where this was still done. Midazolam, which was previously not planned, was added when patient was still uncooperative after meperidine and hydroxyzine were administered, after consent from mother. There were no adverse events that occurred in this case.

5. DISCUSSION

Before chloral hydrate is dismissed as an oral sedation agent in pediatric dentistry, research is required to give validation on the drug's safety and efficacy. Results of this study show that chloral hydrate triple cocktails have higher efficacy and success than the comparable midazolam regimen but with similar safety profiles.
5.1 Safety

The number of adverse reactions that occurred in both regimens was small. There were more adverse reactions with Mid/M/H regimen than in the CH/M/H regimen, but it should be noted that there were also less latter sedations than there were the former. Vomiting was the most frequent adverse reaction in both regimens. Due to the gastric irritability induced by chloral hydrate, one would expect more vomiting with CH/M/H regimens. However, the opposite was true. There were more vomitings with Mid/M/H. It is important to note that meperidine as well as nitrous oxide, drugs that were present in both regimens, are also known to cause nausea and could also contribute to vomiting.

Desaturations occurred more frequently with Mid/M/H. Meperidine, which was present in both regimens, is known to reduce respiratory drive. One would thus expect equal amounts of desaturations. One explanation for the results could be that when chloral hydrate is used as part of a triple cocktail regimen, the amount of meperidine used is generally lowered to ensure a good safety profile.

Over-sedations occurred slightly more in the CH/M/H regimen. Since chloral hydrate is known to cause drowsiness and the half-life is prolonged, over-sedation is expected and data follows suit.

5.2 Efficacy

CH/M/H regimens showed to be the more effective regimen. Fewer procedures were aborted and a high proportion of the sedations were quiet unlike the Mid/M/H regimen where a high proportion of the sedations resulted in crying/screaming behavior. Quiet sedations are expected from chloral hydrate regimens since its prime
characteristic is to induce drowsiness and sleep. The CH/M/H regimen was significantly more effective in ages 9 and under. Unfortunately, the sample size became too small at this point (few children 10 and above were sedated with the either triple regimen) to be useful for analysis.

5.3 Provider experience

Provider’s experience did not make a difference in safety or efficacy. This could be because of two reasons. The first reason is that the one-year difference in resident status is insignificant. At UCSF, Pediatric Advance Life Support (PALS) training is completed in the second year before sedations are attempted. Thus, both second and third year residents should have similar training in rescuing a patient in emergency scenarios. Since adverse events are rare, it may be that third years may not have much more experience dealing with emergencies than second years. Another reason for why there was no difference in safety or efficacy between second and third year providers could be that the number of second year resident cases was insufficient to produce a valid comparison. For example, when comparing safety, there were only 34 2\textsuperscript{nd} year cases versus 236 3\textsuperscript{rd} year cases. When comparing efficacy, there were only 25 2\textsuperscript{nd} year cases versus 117 3\textsuperscript{rd} year cases. This is because it is only in the past couple years that UCSF Pediatric Dental Clinic has decided to allow 2\textsuperscript{nd} years to operate in sedation cases.

5.4 Pre-sedation behavior

Pre-sedation behavior of 1 or 3 did not affect the success of the sedation outcome between the two regimens. However, with a pre-sedation score of 2, CH/M/H regimen resulted is significantly better sedation outcomes. This shows that patient
selection can be key to sedation outcomes. A patient that has moderately cooperative behavior to start with may fare better with the chloral hydrate regimen.

5.5 Limitations of this study

There were several limitations to this retrospective study. If there were duplicate charts present, ensuring that the data for that chart was not duplicated relied on the person doing the chart review to recall something familiar about that chart. Otherwise, the data could have been duplicated. Overall, duplicate charts were rare.

There was often missing data if the operator or monitor for the sedation did not take the time to write down all the details. This is the reason some of the analysis in the study has limited power, including the analysis of provider experience and pre-sedation behavior.

Reversals are sometimes given for learning purposes, rather than due to over-sedation at UCSF. Unfortunately, the clinical notes did not clarify, and it had to be assumed that reversals were given due to over-sedation.

Another limitation of this study was that it was not possible to compare dosages of the medications used in both triple cocktail regimens, even though the weight and dosage was present on each patient. There was far too much variation in the dosages used since each faculty member prefers different dosages.

A confounding factor that could have impacted the results of this study is staggering medications. Staggering is defined as giving oral sedation medication at different times rather than all at once to optimize peak sedation. This is done since no two oral sedation medications have the same duration of effects. For example,
midazolam takes into effect within 15 minutes whereas meperidine and hydroxyzine can take more than 30 minutes, as described in the introduction. Staggering a Mid/M/H sedation regimen might look like this: meperidine and hydroxyzine is delivered orally first, then midazolam is given 15 minutes later. At 30 minutes past the first dosing, all three medications peak in the patient at the same time, giving optimal sedation. This practice has been done more heavily in the recent couple years and could have affected the success of the sedation with the Mid/M/H regimen.

6. CONCLUSION

There was a significant difference in efficacy between the two triple-cocktail regimens, with the CH/M/H regimen showing better behavior outcomes and completion of treatment versus Mid/M/H regimen. There was no significant difference in safety between the two regimens. There was no significant difference in provider’s experience in terms of safety or efficacy. CH/M/H regimen worked significantly better for children age 9 and below. Per this study, as long as sedation guidelines are strictly followed, with the recommended drugs’ dosages used for oral conscious sedation, the chloral hydrate regimen can be safely and effectively used in pediatric dental oral conscious sedation.

Further research is warranted on chloral hydrate’s use in oral sedation. A randomized control prospective trial with standardized dosages will allow a better comparison of the two regimens. A study comparing the outcomes of staggered versus non-staggered Mid/M/H regimens will also show whether onset of these medications must be taken into account when dosing the patient.
7. REFERENCES


8. APPENDIX

8.1 Pre-Sedation Form

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**UCSF Pediatric Dentistry Pre-Sedation Form**

**Today’s Date:** __________/________/________

**Name:** __________________________  **Age:** ______  **Wt:** ______ lbs / kg  **M / F**

**Parent/Guardian:** __________________________

**Ph #:** (________) _______ - _______

**Alt Ph #:** (________) _______ - _______

Available on short notice – YES / NO

---

**Provisional Treatment Plan**

<table>
<thead>
<tr>
<th>Tooth #</th>
<th>Procedure</th>
<th>Tooth #</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Mallampati Classification**

<table>
<thead>
<tr>
<th>Mallampati</th>
<th>Classification</th>
<th>Behavior Scale</th>
<th>Significant Medical Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Soft palate, base of uvula</td>
<td>-may permit x-rays&lt;br&gt;-nitrous oxide not effective&lt;br&gt;-short attn span but coop</td>
<td>Snore? Yes / No</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate, base of uvula</td>
<td>-will not permit x-rays&lt;br&gt;-reaches and grab operator’s hands</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Soft palate, base of uvula</td>
<td>-outwardly uncooperative&lt;br&gt;-restraint required for examination</td>
<td></td>
</tr>
</tbody>
</table>

---

**Initial Check List**

- H & P form given to parent / guardian (Appropriateness for sedation will be determined when H&P is received)
- Discussed NPO rules (Nothing after midnight)
- Informed parent / guardian that sedation may not be successful or the child may require more than one sedation visit
- Informed parent/guardian that they are not permitted in the sedation room during treatment
- Discussed NON-REFUNDABLE sedation fee ($50) and payment envelope given to parent / guardian
- Informed parent/guardian of the wait period (may take up to 2 months for scheduling)
- If patient Cancels apt less than 48 hours than must have physician note for sickness or come to UCSF Pediatric Dental Clinic
- Current contact phone number obtained & Clinic contact phone number given (415-476-3276)

---

**Check List**

- Discussed other pre-operative instructions (i.e. Light clothing, no nail polish, sickness, etc.)
- Consent form given and signed (Please make a copy and put in chart)
- Discussed the use of Papoose Board, N2/O2, voice control, etc.
- Discussed having two adults (parent/guardian and another adult) accompanying the child to the sedation appointment

**Parent/Guardian Signature:** __________________________  **Date:** __________/________/________

---

**Referring Resident** __________________________  **Referring Attending** __________________________
8.2 Pre-Sedation Record
9. UCSF LIBRARY RELEASE

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Author Signature ___________________________ Date 06/09/16