Oral ketamine for pediatric outpatient dental surgery sedation

Elsa C. Alfonzo-Echeverri, DDS Joel H. Berg, DDS, MS Thomas W. Wild, DDS, MS Nancy L. Glass, MD

Abstract

This study compared the sedative effectiveness of orally administered ketamine to a combination of oral meperidine/promethazine (Demerol/Phenergan) in two groups of children. One group received ketamine at a dose of 6 mg/kg and the other group received meperidine/promethazine combination at a dose of 2 mg/kg and 0.5 mg/kg, respectively. All children received nitrous oxide 30–50% titrated to effect. A four-point modification of the Houpt et al.[1] rating scale for the overall behavior was used in the evaluations. The quality of sedation, as rated by subjective measurement of overall behavior (sleep, crying, body movement), was higher in the ketamine group (borderline significance; P = 0.07). Mean onset time was significantly shorter (P < 0.001) for ketamine (20.5 min) than meperidine/promethazine (42.4 min) and postoperative sleep time (recovery) was also shorter (borderline significance; P = 0.08) for ketamine (55.6 min) than meperidine/promethazine (106.8 min). Operative times were similar, but the placement of rubber dam and local anesthetic were slightly better tolerated in the ketamine group. Vomiting was significantly more prevalent (P = 0.05) among those who received oral ketamine. Vital signs were consistent for the two groups with no oxygen desaturation below 95%. (Pediatr Dent 15: 182–85, 1993)

Introduction

Young children sometimes resist dental procedures because of a combination of fear, pain, and anxiety due to their age and/or some type of handicap.[2,3] Although various sedative agents and combinations have been used, most techniques suffer from difficulty or discomfort of administration, lack of efficacy at recommended dosages, unpredictability of response, risk of cardiorespiratory depression and/or prolonged CNS depression.

Sedation for pediatric dental treatment presents special challenges. Although complete immobility is not required, the patient must be cooperative and relatively still, must maintain protective airway reflexes, and must allow the operator to work intraorally. Whereas the procedures may be uncomfortable, pain is attenuated by using local anesthesia prior to the dental procedure. The sedative must not have such a prolonged action that an unresponsive child is sent home from the clinic area.

Despite many recognized limitations, oral administration generally is preferred over parenteral agents for sedation of the difficult pediatric patient.[4] Consistent with reports by Duncan et al.[5] and Houpt,[1] chloral hydrate, alone or as a comedication with hydroxyzine or promethazine, is the most frequently used oral agent (frequently in conjunction with nitrous oxide). Meperidine and promethazine is the second most commonly used drug combination by American Board of Pediatric Dentistry Diplomates.[5]

Ketamine hydrochloride, a phencyclidine derivative, is a safe and effective anesthetic for many procedures.[6] Ketamine HCL, a white crystalline compound that forms a clear colorless solution in water,[7] is a rapid-acting non-narcotic, nonbarbiturate drug with a wide safety margin.[8–10] It is better defined as a dissociative anesthetic with a powerful analgesic effect.[7,9,11] Ketamine differs chemically and pharmacologically from other anesthetic agents and produces a unique anesthetic effect.[9]

The adaptability of ketamine for use in outpatient anesthesia for oral surgery procedures has been reported since 1965.[12] Although its use was initially confined to the operating room, that seems to be changing. Ketamine can be used as an anesthetic or, in lower doses, as a sedative agent.[13–15] Ketamine has several advantages over other anesthetic agents for outpatient dental surgery. It is easy to administer, its onset is rapid, there is a wide margin between therapeutic and toxic doses, and it exhibits a short duration of action.[7,9]

The pharmacokinetics of ketamine in analgesic doses after intravenous, intramuscular, and oral administration have been investigated in healthy volunteers.[16,17] After oral administration, ketamine absorption is incomplete, with only 17% of the dose reaching the systemic circulation because of extensive first-pass metabolism through the liver. The mean peak concentration of 44 ng/ml (range 15–80 ng/ml) was achieved after oral administration of 0.5 mg/kg. The mean time of peak concentration after oral administration is 8 min. Pain threshold elevation occurs at plasma ketamine concentrations above 160 ng/ml.[16,17] The absence of any marked effect after oral administration may be explained by the low plasma concentrations of ketamine, as concentrations did not exceed 80 ng/ml.[17]

Ketamine has a long history of use in pediatric medicine. The successful use of ketamine in the operating room by anesthesiologists managing children with cardiovascular instability led to its acceptance in the cardiac

catheterization lab, where cardiologists continue to use ketamine as the mainstay of sedation for pediatric heart patients. Likewise, children with large burns have been treated with oral, IV, or IM ketamine as an analgesic and sedative for painful burn dressings. Gutstein et al. reported the use of a small dose of oral ketamine, 3–6 mg/kg, as a sedative prior to induction of general anesthesia in order to facilitate separation of the young child from the parents, and to enhance acceptance of the anesthetic mask.[18]

There is little information about oral administration of ketamine for pediatric dental treatment. A report by Badini and Cassarino,[19] based on 12 years of clinical experience, showed successful and safe use of oral ketamine for extractions and outpatient pediatric dental treatment.

Therefore, the aims for the present pilot study were as follows:

1. To evaluate the effectiveness of oral ketamine as a sedative for outpatient dental treatment
2. To compare the sedative effects of ketamine to a commonly used meperidine/promethazine combination
3. To subjectively evaluate and compare child behavior with the two different sedative agents
4. To evaluate the potential use of oral ketamine as a sedative agent for pediatric dental outpatient treatment.

Methods and materials

This protocol was reviewed and accepted by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects (IRB); written informed consent was obtained from the parents of each participant. Forty male and female patients, ranging in age from 20 to 60 months, were selected from the clinic of the Pediatric Dentistry Department at the University of Texas Dental Branch, Houston, Texas. Those children who displayed uncooperative behavior during the initial screening evaluation were considered for entry into the study if they were otherwise healthy (ASA Physical Status I) and had no previous dental experience. Uncooperative behavior included resisting separation from parent, constant loud crying, physically resisting being seated on the dental chair, and refusing to open the mouth for dental examination. Initial attempts at behavioral management prior to designating a child as uncooperative included: interview with the parent and child, desensitization technique (tell, show, do), and positive reinforcement during the examination.

Participants were randomized to receive either oral ketamine 6 mg/kg (20 patients; Ketalar,® Parke-Davis, Division of Warner-Lambert Co. Morris Plains, NJ), or oral meperidine 2.0 mg/kg plus promethazine 0.5 mg/kg (20 patients; Demerol hydrochloride syrup,® Winthrop/Breon, New York, NY; Phenergan syrup fortis,® Wyeth-Ayerst, Philadelphia, PA). Ketamine is not commercially available in an oral form, so the 6 mg/kg dose given to the children in this study was drawn from the parenteral preparation of 100 mg/ml and suspended in 15–30 cc of concentrated grape "Kool-Aid" in an attempt to mask the bitter flavor of the hydrochloride salt. The meperidine/promethazine combination was similarly disguised.

All participants fasted for a minimum of 6 hr. After a physical examination and confirmation of the NPO status, the study drug was administered by a pediatric anesthesiologist in the dental operatory suite. The operating dentist was not aware of which drug the child received. Parents were allowed to remain with the child until transfer to the dental chair, at which time the child was placed on a Papoose Board® (Olympic Medical Corporation, Seattle, WA). The security straps of the Papoose Board remained loose enough to allow for observation of the child's movement and no head restraint device was used. The timing of transfer to the dental chair was determined by the anesthesiologist's observation and judgment about the child's readiness to tolerate the treatment session.

Monitoring the sedated patient throughout the treatment period was performed by the anesthesiologist and dentist using a Dinamap™ vital signs monitor with Oxytrak™ pulse oximeter (Critikon, Inc., Tampa, FL) and a precordial stethoscope. Blood pressure, heart rate, and oxygen saturation were monitored continuously and recorded graphically at 5-min intervals; changes in breath sounds and upper airway sounds also were recorded. Nitrous oxide by nasal mask inhalation at a concentration of 30–50% in oxygen was administered to all children to facilitate local anesthetic infiltration, and was continued in most children for a variable period of time thereafter. A standard dental scavenging system was used to minimize environmental pollution.

All dental restorative procedures were performed using 2% lidocaine with 1:100,000 epinephrine (Astra Pharmaceutical Products, Inc. Westborough, MA). Tolerance of local anesthetic infiltration and rubber dam placement also was recorded as the presence (+) or absence (–) of crying and head movement during these manipulations. Terminating operative time occurred at either the completion of all necessary work or upon the assessment of both dentist and anesthesiologist that the sedation was beginning to wear off and thus would not be sufficient for completion of work on another quadrant of the mouth.

Children were monitored for at least one hour following the procedure until discharge criteria were met. Those criteria included appropriate vital signs for age, presence of protective airway reflexes, ability to tolerate oral fluids, and a return toward preoperative level of consciousness. Although ambulation was not required of all children, those with truncal and cervical ataxia were not allowed to leave until these signs had disappeared.

Discharge instructions, including the name and phone number of the treating dentist, were provided to the parents in the event of problems or concerns. The parents were contacted on the first postoperative day to inquire about sleeping and eating behaviors on the day of the treatment and the occurrence of vomiting, and to address

Table 1. Mean characteristics of ketamine and meperidine/promethazine groups

Variable	N	Ketamine Mean ± SD	N	Meperidine/Promethazine Mean ± SD	t-test t	P
Age (months)	20	40.4 ± 10.2	20	37.5 ± 10.6	0.87	> 0.05
Onset (min)*	20	20.5 5.4	19	42.4 11.2	7.67	< 0.001
Duration (min)*	20	36.4 9.9	16	40.1 15.0	0.87	> 0.05
Recovery (min)†	16	55.6 ± 53.9	14	106.8 ± 92.2	1.83	> 0.05

* N less than 20 in the meperidine/promethazine group due to aborted treatment.
† Not reported by several parents in each group.

any other parental questions. The quality of the sedation was assessed by the operating dentist, who was blinded to the study drug. Subjective observation of the depth of sleep, crying, and body movement was scored using a modification of the rating scale developed by Houpt et al.[1] as follows: 1) ABORTED — treatment could not be initiated because of excessive crying and/or movement, despite repeated efforts, 2) POOR— treatment was frequently interrupted, and limited by such behaviors, 3) FAIR—all planned treatments were accomplished, despite brief, intermittent movement and/or crying, and 4) GOOD — all planned dental treatment was completed without crying or movement.

Results

There were no episodes of cardiorespiratory depression, oxygen desaturation below 95%, airway compromise, laryngospasm, bronchospasm, or excessive oral secretions with either sedative regimen. There were also no reports of dysphoric reactions or nightmares.

Mean characteristics of the two study groups and a *t*-test analysis of intergroup mean differences are given in Table 1. Differences in age and duration of the operative procedure were not statistically significant. Sedation onset time for ketamine was less than half that of meperidine/promethazine and the difference was highly significant ($P < 0.001$). Recovery time in the ketamine group was also only about half that observed in the meperidine/promethazine group, but due to the high degree of variability in each group (range: 0 – 5 hr), the difference in means was of borderline significance only ($P = 0.08$). Most of the children who received ketamine were awake and active after postoperative recovery times up to 2 hr, with one child sleeping for 3 hr. In the meperidine/promethazine group three children slept from 3.8 to 5 hr postoperatively.

As can be seen in Table 2, ketamine produced better overall sedation scores than the meperidine/promethazine group. Although the distribution of scores was only of borderline significance by chi-square analysis ($P = 0.07$), an important clinical observation was the fact that no treatments had to be aborted in the ketamine group, while dental treatment in four (20%) of the meperidine patients could not be initiated. Additionally, whereas 13 of 20 patients (65%) receiving ketamine exhibited good sedation, only 9 of 20 patients (45%) receiving meperidine/promethazine were considered to have good sedation.

Although better tolerance of the anesthetic injections and rubber dam placement (absence of crying or moving) was observed in the ketamine group, the differences were not statistically significant (Table 3). A significantly ($P = 0.05$) greater frequency of vomiting was observed among those who received oral ketamine (40%) compared with those who received meperidine/promethazine (5%). Four of the eight patients who vomited in the ketamine group did so during the operative procedure, and four postoperatively. No patient had more than one episode of vomiting or suffered adverse airway or pulmonary consequences.

Discussion

The aim of using sedative drugs in pediatric patients is

Table 2. Overall quality of sedation (frequency) observed in ketamine and meperidine/promethazine group

Quality Scale*	Ketamine N	Ketamine %	Meperidine/Promethazine N	Meperidine/Promethazine %
Sedation aborted	0	0.0	4	20.0
Poor sedation	6	30.0	3	15.0
Fair sedation	1	5.0	4	20.0
Good sedation	13	65.0	9	45.0

* Modified from 6-point scale of Houpt et al. (1985), and based upon subjective evaluation of side effects (see Table 3), movement during the operative procedure and smoothness and duration of recovery. Chi-square analysis indicated borderline significance ($P = 0.07$; $x^2 = 7.53$; df = 3) of ketamine vs. demerol/phenergan.

Table 3. Frequency of treatment-related behaviors and side effects

Side Effect and/or Behavior	Ketamine yes	Ketamine no	Meperidine/Promethazine yes	Meperidine/Promethazine no	Chi-square Analysis x^2	Chi-square Analysis P
Crying during rubber dam placement	3	17	5	11	1.36	> 0.05
Crying during local anesthetic injection	6	14	8	12	0.44	> 0.05
Vomiting during or after sedation	8	12	1	19	5.16*	0.05

* With Yates correction.

to diminish fear, pain, and anxiety, thereby creating behavior that will facilitate the provision of quality care. This will help the child get through a difficult treatment without a negative psychological response and help the child learn to cope with future treatment in the dental office.

An ideal sedative for pediatric outpatient dental procedures would be effective, easy to administer, have a rapid onset, and be inexpensive. Most importantly, it would carry minimal risk of cardiorespiratory depression or prolonged CNS depression. These are some of the characteristics that ketamine possesses. Other advantages include a wide margin of safety between therapeutic and toxic doses and its analgesic properties (high safety and therapeutic index). Despite these excellent attributes, there seems to be very little information in the literature on using oral ketamine for pediatric patients undergoing dental treatment.

The results of our preliminary study indicate that ketamine, 6 mg/kg orally, provides safe, high-quality sedation for young children undergoing outpatient dental surgery procedures. This is the dosage recommended by Gutstein et al. as a preanesthetic medication in children.[18] The rapid onset, short postoperative sleep times, and absence of aborted treatments (wasted appointments) are clinically relevant to dentists and parents alike. Since a palatable, well-tolerated vehicle for the ketamine (concentrated grape flavored, sugar-free soft drink mix), was not decided upon until the later stages of the study, it is possible that some of the vomiting may have been related to our initial vehicles. Two additional factors that could have contributed to the vomiting episodes were initial high concentration of N_2O/O_2, and absence of a true empty stomach. It is interesting to note that parenteral administration of ketamine in pediatric dental patients also has been associated with nausea in 22% and vomiting in 15% of the patients.[20]

Further studies are in progress or being planned to examine absorption rates, effects of varying doses in children, and other factors possibly related to the vomiting. Preliminary unpublished data indicate that by controlling initial concentration of N_2O/O_2 and ensuring compliance with NPO status, the incidence of vomiting episodes related to the oral ketamine sedation may be reduced. [21]

Conclusion

1. Ketamine, orally at 6 mg/kg provided more rapid onset of sedation (P = 0.001) as compared to a combination of 2 mg/kg meperidine and 0.5 mg/kg promethazine HCL orally.
2. Differences of borderline significance were observed between the two regimens for recovery (P = 0.08) and overall quality of sedation (P = 0.07) and no statistically significant differences were noted for duration, placement of rubber dam or local anesthetic injection.

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Dr. Alfonzo-Echeverri is assistant professor, Dr. Berg is associate professor, and Dr. Wild is associate professor, Department of Pediatric Dentistry and Pediatrics, University of Texas Health Science Center, Houston, Texas. Dr. Glass is associate professor in anesthesiology and pediatrics, and adjunct assistant professor in pediatric dentistry, Baylor College of Medicine, Houston, Texas.

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