A Comparison Study Between Ketamine and Ketamine-Promethazine Combination for Oral Sedation in Pediatric Dental Patients

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This study compared the incidence of vomiting and the sedative effectiveness of ketamine to a ketamine-promethazine combination in pediatric dental patients. Twenty-two patients with American Society of Anesthesiologists' classification I physical status who were between the ages of 21 and 43 months were randomly divided into 2 groups. The control group received 10 mg/kg of ketamine orally, whereas the experimental group received 10 mg/kg of ketamine and 1.1 mg/kg of promethazine orally. Nitrous oxide in oxygen was supplemented between 35 and 50%. Each patient received 1 or 2 quadrants of restoration by one operator. Heart rate, blood pressure, and oxygen saturation were monitored and recorded during the treatment. Crying, alertness, movement, and overall general behavior were rated using the scale by Houpt et al. A dentist-anesthesiologist conducted the vital sign monitoring and behavioral assessment. Ketamine combined with promethazine eliminated the incidence of vomiting. A 2 × 2 chi-square contingency table showed a statistical difference between the 2 groups at $P < .05$ (control group, 27%; experimental group, 0%). Ketamine alone yielded better sedations than the combined agents as shown by the Mann-Whitney U statistical analysis ($P < .05$). Ketamine and a ketamine-promethazine combination are effective in the sedation of pediatric dental patients.

Key words: Oral sedation; Oral ketamine; Dentistry.

Ketamine is a dissociative anesthetic agent that has been shown to be useful as a safe and effective oral sedative.[1–8] The drug was first derived in 1961, and reports on human trials were begun in 1965. It is a chemical derivative of phencyclidine and cyclohexamine.[9] Ketamine is unique in being effective for induction of anesthesia by either the intravenous or the intramuscular route; however, only recently has the drug been studied in subanesthetic sedative doses per oral administration. Patients who are given anesthetic doses of ketamine may appear to be awake with open eyes, yet are unaware of the environment and do not experience pain. This response is termed dissociative anesthesia, during which patients independently and continuously maintain their protective reflexes and may or may not respond appropriately to verbal or painful stimulation, depending on the level of dissociation. Patients often exhibit nonpurposeful movement independent of the stimulation. In the central nervous system, dissociative anesthesia is characterized by electroencephalographic evidence of dissociation between the limbic system and the thalamus. Ketamine also produces intense analgesia, which can be explained in part by specific suppression of the spinal cord activity necessary for transmission of pain to the higher brain centers.[10] Anterograde amnesia is intense, which may be a beneficial effect in the consciously sedated patient. Nystagmus associated with ketamine often heralds the onset of dissociative sedation. Although nystagmus may preclude the use of the drug for operations or examinations of the eyes, this

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side effect is of little importance in the dental patient. Emergence delirium, including dreams and hallucinations,[11,12] ranges from 5–30%, with an increased incidence reported in patients older than 16 years, female patients, patients taking high intravenous doses (>2 mg/kg), and patients with a history of personality problems or frequent dreaming. Emergence delirium can also be attenuated with concomitant use of a benzodiazepine agent.[10] Other central nervous system effects include an increase in cerebral blood flow and subsequent increase in intracranial pressure. This ketamine-induced activity is unlikely to precipitate convulsions in patients with seizure disorders and does not alter the seizure threshold in epileptic patients.[10]

Ketamine produces cardiovascular effects that resemble a centrally mediated sympathetic stimulation. Although the mechanisms are complex, intravenous anesthetic induction doses show increases in systemic and pulmonary arterial blood pressure, heart rate, cardiac output, cardiac work, and myocardial oxygen requirement. The use of ketamine should probably be avoided in patients with severe hypertension, coronary disease, or congenital heart diseases that compromise cardiac function and reserve. However, this relative contraindication represents an insignificant portion of the pediatric dental population. Ketamine maintains an intact protective airway reflex, resulting in an incidence of aspiration that is minimal.[13] Since ketamine causes both bronchodilation and maintenance of upper airway skeletal muscle tone, it is indicated for the asthmatic patient. Ketamine has not been shown to significantly alter hepatic or renal function, and since it does not stimulate the release of histamine, it rarely causes allergic reactions.

Advantages of using ketamine as an oral sedative agent for pediatric dental patients include a relatively fast onset (25 minutes) in part due to its extreme lipid solubility and rapid transfer across the blood-brain barrier, analgesia and sedative effects, minimal respiratory depression,[9] a wide safety margin, and adequate operating time (36.4 minutes).[2] The literature reports oral doses of ketamine ranging from 4–10 mg/kg. However, the 10-mg/kg oral dose in this study was selected after patients in trial runs at 8 mg/kg did not reach the desired level of sedation. Promethazine is a potent antihistamine that is useful in dentistry as a sedative, an antiemetic, and an antisialagogue.[14] Promethazine is widely used with meperidine as an adjunct to increase the sedative effect and to minimize the nausea frequently encountered with meperidine in pediatric dental patients. The antisialagogue effect of promethazine may also prove beneficial in avoiding the potential cough and laryngospasm associated with the excessive salivation[13] sometimes seen with ketamine. The addition of promethazine may also enhance the working time needed for longer operative procedures. Since nausea and vomiting have been implicated with ketamine use alone,[2,11,12,15] this study will evaluate the frequency of vomiting using a ketamine-promethazine combination compared with ketamine alone.

The purposes of this study were to compare the sedative effectiveness of orally administered ketamine to a ketamine-promethazine combination to evaluate the incidence of vomiting and to determine if ketamine-promethazine is an effective combination in managing uncooperative pediatric dental patients.

MATERIALS AND METHODS

Pediatric dental patients from the Houston Medical Center Pediatric Dental Clinic, Houston, Tex, were chosen for the study, which was approved by the Committee for the Protection of Human Subjects. The selection criteria included healthy patients between 1½ and 3½ years of age with no previous dental experience and those who demonstrated such poor behavior at the initial dental examination that they were deemed to need oral sedation for subsequent restorative visits. Poor behavior included crying, apprehension, uncooperation for the examination and cleaning, poor response to behavioral management techniques and verbal commands, and physical resistance. Risks and benefits of the sedation followed by the presedation instructions were explained to the parent at the initial examination appointment. The patients had taken nothing by mouth for at least 8 hours before the procedure. A written consent form was obtained for each parent or guardian at the initial appointment.

Twenty-two male and female patients participated, with 11 patients in the control group and 11 patients in the experimental group. Preoperative vital signs, including heart rate, blood pressure, and oxygen saturation, were obtained. The control group received 10 mg/kg of body weight of ketamine orally (Ketalar; Parke-Davis, Morris Plains, NJ), whereas the experimental group received 10 mg/kg of ketamine and 1.1 mg/kg of promethazine orally (Phenergan syrup fortis; Wyeth-Ayerst, Philadelphia, Pa). Each regimen was disguised in 5 mL of Syrpalta (Emerson Laboratories, Texarkana, Tex), a concentrated, grape-flavored syrup, to mask the bitter taste of ketamine. The study was conducted in a double-blind fashion. The operator, the dentist-anesthesiologist, and the subjects did not know which regimen was selected. A third person randomly selected the drug regimen and administered it to the patients. After the drug administration, the patient remained in the waiting room with the parent until ready for treatment. At 25

Table 1. Rating Scale for Crying, Alertness, and Movement

Score Crying	*Alertness*	*Movement*
1 Hysterical crying	Fully awake, alert	Violent, interrupting treatment
2 Continuous or strong crying	Drowsy, disoriented	Continuous, making treatment difficult
3 Intermittent or mild crying	Asleep	Controllable, not interfering with treatment
4 No crying	—	No movement

minutes, each patient was brought to the operatory and placed onto the Papoose Board (Olympic Medical Corp, Seattle, Wash). The patient was monitored with a precordial stethoscope, pulse oximeter (Mini Pack 911-ST, Pace Tech, Clearwater, Fla), and blood pressure cuff. A total of 50% N_2 O-O_2 was used at 3 L/min of total gas flow for the first 5 to 10 minutes. After the local anesthetic was given, the nitrous oxide was reduced to 35% for the remainder of treatment. A total of 100% oxygen was given during the last 5 minutes of the appointment. The patient received either 1 or 2 quadrants of restoration, including alloys, pulpotomies, and stainless steel crowns. All treatment was performed with rubber dam isolation. One operator performed the dental treatment on all of the patients. The dentist-anesthesiologist recorded the heart rate, oxygen saturation, and blood pressure at 5-minute intervals and also evaluated the patients for crying, alertness, and movement (Table 1) at each of the following intervals: (a) parental separation; (b) placement onto Papoose Board; (c) placement of nasal mask and monitors; (d) local anesthetic administration; (e) placement of rubber dam and bite block; (f) initiation of treatment; and (g) 15-minute intervals until completion of treatment.

The overall general behavior of each patient was assessed by the operator and dentist-anesthesiologist immediately after the completion of the treatment, using the rating scale by Houpt and coworkers[1] consisting of 6 behavior classifications (Table 2).

After the treatment, each patient was returned to the parent and remained in the waiting room for up to 1 hour. The patient's physical status and alertness were assessed before discharge. Each patient had to be able to respond to verbal commands, be alert or easily arousable, breathe spontaneously, be able to walk with minimal assistance, and be accompanied by a responsible adult before being dismissed. A follow-up telephone call was made by the operator the same evening to determine the patient's condition.

Table 2. Rating Scale for General Behavior

1 Aborted	No treatment rendered
2 Poor	Treatment interrupted, only partial treatment completed
3 Fair	Treatment interrupted but eventually all completed
4 Good	Difficult but all treatment performed
5 Very good	Some limited crying or movement, eg, during anesthesia or mouth prop insertion
6 Excellent	No crying or movement

Using the Mann-Whitney *U* test, the difference in the general behavior was evaluated. The chi-square test was used to compare the vomiting frequencies and the Student's *t* test was used to compare the difference in total time in the operatory between the 2 groups.

RESULTS

The age range of the subjects was 21–43 months, with a mean age of 33½ months. There were no significant differences in age (for controls, range, 21–43 months; mean, 33 months; for experimental patients, range, 25–43 months; mean, 34 months) (Table 3). Under the conditions of this study, the average time in the operatory, from placement onto the Papoose Board until treatment completion, was not significantly different between the 2 groups using the Student's *t* test at $P = .05$ (Table 3). In the control group (ketamine only), 3 (27%) of 11 patients vomited. The first patient had one episode of vomiting during the treatment procedure and once when she left the office. The second patient vomited once when he left the office. The third patient vomited once approximately 15 minutes after receiving the ketamine. These patients vomited varying small amounts of clear liquids. In the experimental group (ketamine and promethazine), none of the subjects experienced vomiting (0%). A 2 × 2 chi-square contingency table showed that there was a statistically significant difference in the vomiting frequencies between the 2 drug regimens at $P <. 05$.

For both groups, most of the patients drank the liquids willingly and tolerated the taste quite well. Four of the patients refused any oral intake and were administered the premedication using a Monoject syringe. Also, in both groups most of the patients were drowsy or asleep and exhibited no crying or movement at 25 minutes when they were separated from the parents. For the local anesthetic administration, approximately half of the control and half of the experimental subjects did not cry, whereas the other half exhibited intermittent to strong

Table 3. Comparisons Between Experimental and Control Groups

Variable	*Experimental Group (n = 11)*	*Control Group (n = 11)*
Age, mean ± SD	34 ± 6.28	33 ± 6.65
(range), mo	(25–43)	(21–43)
Sex	Males = females	Males = females
Time in operatory, mean ± SD	33 ± 11.87	30 ± 6.12
(range), min	(10–50)	(20–42)
Vomiting, No. (%)	0 (0)	3 (27)
General behavior score, mean ± SD	3.12 ± 0.29	4.27 ± 0.5

crying. Most remained drowsy and about half of the patients were awake. There was an increase in body movement, however, in more than half of the patients, and the movement was rated by the anesthesiologist observer as controllable and not interfering with the local anesthetic administration. At the initiation of treatment, more patients were crying in the experimental group than in the control group. In both groups, most of the patients were drowsy and only a few were fully awake. A greater number of patients exhibited continuous movement in the experimental group than in the control group.

The control group yielded more effective sedations than those seen in the experimental group. There were more control patients rated in the good and very good categories, whereas the experimental patients were more distributed in the fair and good categories (Table 3). Each group yielded one excellent sedation. Of the total participants, only one case (experimental group) was aborted due to the patient's violent physical movement and crying, rendering the treatment impossible. The patient was rescheduled to have the dental treatment performed under general anesthesia. The difference in the general behavior between the 2 groups was statistically significant as demonstrated by the Mann-Whitney U test at $P = .05$. The pulse and blood pressure measurements were within a normal range from baseline for each patient. Oxygen saturation levels were maintained between 97–100%. One patient had a transient drop of the oxygen saturation from 99–95% halfway through the treatment, but it quickly returned to 97%. There were no clinically significant differences in saliva production between the experimental group and the control group and no other apparent adverse effects on either patient group as a whole.

DISCUSSION

Ketamine has been used as an oral sedative in the management of uncooperative patients. Common side effects of ketamine are nausea and vomiting, which have been reported in 0–43% of patients.[16] In this study, the addition of promethazine, a potent antiemetic drug, reduced the vomiting incidence from 27% (control group) to 0% (experimental group).

Patients given oral ketamine achieved sedation in approximately 25 minutes as evidenced by their drowsiness when separated from the parents and the presence of a blank stare. The blank stare and nystagmus are typical effects seen with ketamine administration. It should be noted that some of the parents who were unfamiliar with ketamine sedation were not totally comfortable seeing their child sedated and demonstrating a blank stare and nystagmus. Explaining to the parents the expected clinical side effects of ketamine, especially about the nystagmus, is helpful in making them more at ease and relieving unnecessary anxieties.

One patient from the control group (3½ years old) said that she had a nightmare after the dental treatment was completed. The parent also reported later that the patient complained of nightmares while she was in the waiting room after she was given the ketamine. After the appointment, the parent did mention that the child had a history of nightmares and that she would sometimes wake up at night crying.

The follow-up telephone calls revealed that most patients slept after returning home. The postoperative drowsiness and sleep for both groups ranged from 15 minutes to 6 hours, with an average of 3 hours. However, these data were obtained subjectively from the parents by their recall and were not precisely measured. The sleep pattern as reported by the parents appeared to be intermittent, with periods of wakefulness in between. There were no other adverse problems except for the incidences of vomiting previously discussed.

CONCLUSION

The results of the general behavior rating between the 2 groups were not as expected. There was a trend for promethazine to decrease in incidence the vomiting, but it did not improve the sedation in the study group as might be assumed. At this time, the presumed pharmacological interaction between ketamine and promethazine is not known. It is questionable whether pro-

methazine may reduce the sedative effect of ketamine. The small patient sample in this preliminary study may have influenced the statistical outcome of the study as well. It may be speculated that a larger patient sample could possibly yield different results. It has been suggested that the addition of a different antiemetic agent to ketamine may produce a different result from that obtained from this study. Since hydroxyzine is also used in pediatric dentistry as a mild sedative and as an antiemetic drug, its combination with ketamine has potential merits and a future clinical evaluation is warranted.

From this study, ketamine provided good to excellent sedations in most patients. Promethazine appeared to decrease the vomiting when added to ketamine. The combination of ketamine and promethazine yielded adequate sedations but was not as effective as ketamine alone.

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