

Evaluation of the sedative effect of intranasal versus intramuscular ketamine in 2–6-year-old uncooperative dental patients

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Abstract

Background. Conscious sedation has gained more popularity these days, with different routes of drug administration having various advantages and disadvantages. Among all, ketamine is one of the most commonly used drugs in children.

Objectives. The aim of the present study was to compare 2 different routes of ketamine administration – intranasal (IN) vs. intramuscular (IM) – in 2–6-year-old uncooperative children needing dental treatment.

Material and methods. This single-blind, crossover clinical trial was conducted on a group of 26 uncooperative children aged 2–6 years, who required at least 2 similar dental treatment visits. The patients were randomly assigned into 2 groups: group I – IN ketamine at their 1st session and IM ketamine at the 2nd session; and group II – exactly the opposite sequence. The sedative efficacy of the 2 techniques was assessed by 2 independent pediatric dentists based on the Houpt sedation rating scale. The data was analyzed using the Wilcoxon test, the repeated measures analysis of variance (ANOVA) and the least significant difference (LSD) test.

Results. The participants showed reduced crying and movement with improved sleepiness at the 3 time points examined when IM administration was performed as compared to IN sedation ($p < 0.05$). The overall behavior scores were higher for the IM route as compared to the IN route at all tested time points ($p < 0.05$). The operating dentist and the parents believed that the IM route was significantly more effective ($p < 0.05$). The children in the IN session reached equilibrium faster than those in the IM session ($p < 0.05$). No significant statistical differences were noted between the groups with regard to various physiological parameters investigated at different time intervals.

Conclusions. Intramuscular ketamine was more satisfactory and effective than the IN route when sedating uncooperative children for dentistry.

Keywords: intranasal, children, dentistry, sedation, intramuscular

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Introduction

The anxiety-provoking nature of dental treatment and the incomplete development of coping skills in children have turned behavior management problems into one of the most common challenges that pediatric dentists face in their routine practice.^{1,2} Dental fear and anxiety are considered one of the main obstacles to successful dental treatment in pediatric dentistry, which can directly affect the quality of dental care.³ Children aged 3–7 years tend to be more uncooperative,⁴ with a decreasing trend based on age.⁵

Both pharmacological and non-pharmacological modes of behavior management have been recommended by the American Academy of Pediatric Dentistry (AAPD).⁶ Considering changes in the society and individual attitudes toward traditional physical restraints, the pharmacological behavior management techniques have gained more popularity.¹ Pharmacological management is a broad term that describes the use of drugs to manage the behavior of pediatric patients during dental treatment; it is divided into 2 subcategories – sedation and general anesthesia.⁷ Conscious sedation is an advanced behavior management technique indicated in children with low coping capacity, including children with behavior management problems, dental fear and anxiety, mental retardation, or psychiatric conditions.⁸

Various routes, such as oral, intranasal (IN), intramuscular (IM), intravenous (IV), subcutaneous, and inhalation, have been introduced for sedative drug administration.⁹ The IN technique is a fast, painless and non-invasive method of drug administration that is occasionally used in pediatric dentistry, especially for young children. The selected medication is sprayed or dripped into the nostrils; it is expected to be absorbed directly into the bloodstream, bypassing the gastrointestinal tract and hepatic metabolism, as in the case of the oral medication delivery route.^{1,10} There are reports of a burning sensation following IN administration, which can be minimized by the use of a topical anesthetic spray prior to sedative drug administration.¹⁰ When comparing the sedative effects of different routes, it is important to consider the bioavailability of the drug. The bioavailability of nasally administered ketamine in children has been reported to be approx. 50%, whereas the bioavailability of IM administered ketamine is approx. 93%.^{11,12}

Various medications are used for conscious sedation, either as a single drug or in combination to produce synergistic action. Ketamine is a highly effective sedative drug with a broad margin of safety, resulting in a dissociative state, sedation, analgesia, and amnesia, with the preservation of spontaneous respiration and airway reflexes, and without respiratory depression¹⁰ when used at the recommended doses. Subanesthetic

doses of ketamine (0.5–1.0 mg/kg) provide sedation and analgesia.^{13,14} Ketamine is safe and effective when using the IN route to produce moderate sedation for providing dental care to pediatric dental patients.¹⁵ Nausea and vomiting are common postoperative complications associated with this medication.¹⁶ Postoperative hallucinations have been reported in ketamine cases, leading to its more limited administration, although such side effects occur much less frequently in children.¹⁴

The present study was conducted to compare IN vs. IM ketamine in a group of 2–6-year-old uncooperative children for dental treatment.

Material and methods

This single-blind, crossover clinical trial was conducted on 26 uncooperative 2–6-year-old children with definitely negative or negative Frankl scores, who were referred to the Pediatric Dentistry Fellowship Clinic at the Dental School of Shahid Beheshti University of Medical Sciences, Tehran, Iran, and required at least 2 similar dental treatment visits. Children with nasal obstruction, respiratory infections, limitations in neck movement, macroglossia, tonsil hypertrophy, micrognathia, or limitations in mouth opening were excluded. The subjects were included if they were classified as ASA I, according to the American Society of Anesthesiology (ASA).

Ethics approval was obtained from the Ethics Committee of the Dental Research Center at Shahid Beheshti University of Medical Sciences (2013-7-ResCom-0011-approved). The parents of the subjects signed a written informed consent form. The nil per os (NPO) period was instructed as no solid foods for 8 h and no clear liquids for 2–3 h prior to sedation.

The children were randomly assigned into one of the 2 groups – group I or group II. Both groups received a midazolam vial (2.5 mg/mL; Dales Pharmaceuticals Ltd., Skipton, UK) at a dosage of 0.5 mg/kg and atropine (0.5 mg/mL; Caspian Tamin Pharmaceutical Co., Tehran, Iran) at a dosage of 0.02 mg/kg, given orally as a pre-medication. The medications were prepared and administered under the direct supervision of the anesthesiologist in charge. All basic information was recorded, including age and weight, along with vital signs.

Group I received midazolam orally as a pre-medication 45 min before 1 mL of 2% lidocaine hydrochloride (ampule 2%; Pasture Institute of Iran, Tehran, Iran) was administered into one of the nostrils by using a syringe to obtain relative analgesia and prevent a burning sensation in the nasal mucosa. Then, after waiting 1 min, a total of 10 mg/kg of ketamine (ampule 50 mg/mL; Rotexmedica, Hamburg, Germany) was administered

into the nostrils with a syringe. Group II received an injection of ketamine into the gluteal muscle at a dosage of 5 mg/kg. All participants were subjected to the other method at their 2nd session.

Upon the onset of sedation and the dissociative effects of ketamine (closed eyes or nystagmus, sleepiness or irresponsiveness to tactile or verbal stimuli, or vague and irrelevant answers^{17,18}), supplemental oxygen was administered via a nasal cannula at 2 L/min before the initiation of dental treatment.

Physiological parameters, including the heart rate (HR), blood oxygen saturation (SpO₂), blood pressure (BP), and the respiratory rate (RR), were recorded using a portable monitoring device (Saadat, Tehran, Iran) at baseline, after anesthesia administration, at 15 and 30 min from the start of treatment, and at discharge.

An independent pedodontist judged the level of sedation in all cases at 3 time points – at local anesthesia administration, and at 15 and 30 min from the start of treatment – using the Houpt sedation rating scale (Table 1).¹⁹ The details of the Houpt scale include crying (C), sleep (S), movement (M), and overall behavior (O).

After the completion of treatment, the child was transferred to the recovery room, where constant monitoring was conducted for the next 2 h. The children were discharged when they were judged as responsive to verbal and tactile stimuli. They should have no signs of abnormal breathing while being fully awake, and be able to talk, grasp their hand, or sit and stand. Discharge was declared in the presence of the child's parents and upon the approval of the anesthesiologist.¹⁸

The potential postoperative side effects, including nausea, fever, restlessness, headache, dizziness, a decrease or an increase in activity, and flushing, were checked for 12 h postoperatively. The parental overall satisfaction was also recorded through a phone conversation 24 h after each session.

Statistical analysis

The data was analyzed using the Wilcoxon test, the repeated measures analysis of variance (ANOVA) and the least significant difference (LSD) test to compare the redundancy of the items with regard to the crossover design of the study.

Table 1. Houpt scale criteria at different time intervals for intranasal (IN) and intramuscular (IM) ketamine administration

Route of drug administration	Sedation score by Houpt et al. ¹⁹	Local anesthesia administration				15 min from the start of treatment				30 min from the start of treatment			
		C	S	M	O	C	S	M	O	C	S	M	O
IN ketamine	1	0 (0.0)	4 (15.4)	0 (0.0)	1 (3.8)	0 (0.0)	6 (23.1)	2 (7.7)	12 (46.2)	0 (0.0)	6 (23.1)	2 (7.7)	14 (53.8)
	2	7 (26.9)	19 (73.1)	12 (46.2)	0 (0.0)	21 (80.8)	19 (73.1)	20 (76.9)	5 (19.2)	22 (84.6)	20 (76.9)	21 (80.8)	7 (26.9)
	3	15 (57.7)	3 (11.5)	11 (42.3)	4 (15.4)	4 (15.4)	1 (3.8)	3 (11.5)	4 (15.4)	4 (15.4)	0 (0.0)	3 (11.5)	1 (3.8)
	4	4 (15.4)	–	3 (11.5)	16 (61.5)	1 (3.8)	–	1 (3.8)	3 (11.5)	0 (0.0)	–	0 (0.0)	4 (15.4)
	5	–	–	–	4 (15.4)	–	–	–	1 (3.8)	–	–	–	0 (0.0)
	6	–	–	–	1 (3.8)	–	–	–	1 (3.8)	–	–	–	0 (0.0)
IM ketamine	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	6 (23.1)	0 (0.0)	0 (0.0)	3 (11.5)	10 (38.5)	5 (19.2)	0 (0.0)	6 (23.1)	18 (69.2)	12 (46.2)	0 (0.0)
	3	3 (11.5)	20 (76.9)	8 (30.8)	0 (0.0)	5 (19.2)	16 (61.5)	12 (46.2)	2 (7.7)	15 (57.7)	8 (30.8)	12 (46.2)	2 (7.7)
	4	23 (88.5)	–	18 (69.2)	1 (3.8)	18 (69.2)	–	9 (34.6)	4 (15.4)	5 (19.2)	–	2 (7.7)	10 (38.5)
	5	–	–	–	7 (26.9)	–	–	–	10 (38.5)	–	–	–	10 (38.5)
	6	–	–	–	18 (69.2)	–	–	–	10 (38.5)	–	–	–	4 (15.4)

Data presented as number (percentage) (n (%)).

Houpt scale criteria: C – crying (1 – hysterical crying; 2 – continuous or strong crying; 3 – intermittent or mild crying; 4 – no crying); S – sleep (1 – fully awake, alert; 2 – drowsy, disoriented; 3 – asleep); M – movement (1 – violent, interrupting; 2 – continuous, making treatment difficult; 3 – controllable, not interfering with treatment; 4 – no movement); O – overall behavior (1 – aborted, no treatment rendered; 2 – poor, treatment interrupted, only partial treatment was completed; 3 – fair, treatment interrupted, but eventually completed; 4 – good, difficult, but all treatment was performed; 5 – very good, some limited crying or movement; 6 – excellent, no crying or movement).

Results

The data was collected from 26 children (15 boys and 11 girls) aged 2–6 years, with a mean age of 39.8 months and a mean weight of 14.6 kg. In total, 15 patients (57.7%) scored definitely negative, and 11 (42.3%) scored negative according to the Frankl's behavior rating scale (FBRs).⁷

According to the Wilcoxon signed-rank test, the child's acceptance rate of the IN route was higher as compared to the IM route. Five children took the drug reluctantly, but without resistance, through the IN route, while all children resisted taking the medicine via the IM route.

The drug onset time was 5–10 min and its action lasted for 35–60 min (48.3 min on average) for the IN route, while for the IM route, the duration was 5–20 min (13.2 min on average) and 60–90 min, respectively, with the difference being statistically significant ($p < 0.05$).

According to the Wilcoxon signed-rank test, the Houpt scale scores were significantly different between the 2 groups at the time of administration, and after the first and second 15 min. The children cried less, had a deeper sleep and showed fewer movements in the case of the IM route as compared to the IN route at all 3 time points ($p < 0.05$) (Tables 1 and 2).

For the IN route, the most frequent scores with regard to the overall behavior were 4 (good) at the time of administration, and 1 (aborted) at 15 min and 30 min from the start of treatment. For the IM route, the most frequent overall behavior scores were 6 (excellent) at administration, 5/6 (very good/excellent) after the first 15 min and 4/5 (good/very good) after another 15 min. The Wilcoxon test showed statistically significant differences between the 3 time points. The success rate in terms of sedation and ease of treatment was higher in the IM session as compared to the IN session at all 3 time points ($p < 0.05$) (Tables 1 and 2).

In addition, the operating dentist believed that the IM route was significantly more effective than the IN route

($p < 0.05$). The parents also preferred the IM route and believed that it was much more effective ($p < 0.05$). The children in the IN session reached equilibrium (the discharge status with independent normal walking) faster than those in the IM session, and the difference was statistically significant ($p < 0.05$).

The side effects of ketamine included flushing, abnormal muscle tone and emergence reactions in both groups during treatment and before discharge, with the differences between the groups not reaching significance ($p > 0.05$) (Table 3). The most commonly reported post-treatment complications were vomiting and flushing in both groups; 12 patients in the IN session and 11 patients in the IM session reported some sort of vomiting post-operatively, with the difference between the groups being non-significant ($p = 0.317$). Five patients in each group showed signs of flushing, which was not statistically significant ($p > 0.05$) (Table 3). Visual disturbances, desaturation and behavioral abnormalities were not observed in either of the groups.

Considering the overall behavior scores, 4, 5 and 6 on the Houpt scale indicate successful sedation. The Wilcoxon test showed no significant difference in the success rate of the 2 different routes at the time of drug administration, while after the first and second 15 min, the IM route was statistically more effective ($p < 0.05$) (Table 2).

The repeated measures ANOVA and the LSD test showed that the differences in physiological parameters (HR, SpO₂, BP, and RR) were not statistically significant between the groups and within the groups. The mean HR in each group was at its lowest at baseline and increased insignificantly in the IN session at the subsequent time points, while the changes in the IM session were significant. There were no significant differences in HR between the 2 groups at baseline, after anesthesia administration, 15 min after starting the treatment, and at discharge, while HR was significantly higher in the IM session 30 min after starting the treatment.

Table 2. Successful sedation at different time intervals for intranasal (IN) and intramuscular (IM) ketamine administration (Wilcoxon test)

Route of drug administration	Local anesthesia administration	15 min from the start of treatment	30 min from the start of treatment	Wilcoxon test (child acceptance)	Wilcoxon test (onset time)	Wilcoxon test (overall behavior)
IN ketamine	21 (80.8)	5 (19.2)	4 (15.4)	$p > 0.05$	$p < 0.05$	$p < 0.05$
IM ketamine	26 (100.0)	24 (92.3)	24 (92.3)			

Data presented as n (%).

Table 3. Complications and side effects of intranasal (IN) and intramuscular (IM) ketamine administration

Route of drug administration	During treatment and before discharge				Post-treatment		
	flushing	abnormal muscle tone	emergence reactions	no complications	no vomiting	vomiting once	vomiting twice
IN ketamine	5 (19.2)	4 (15.4)	4 (15.4)	13 (50.0)	14 (53.8)	10 (38.5)	2 (7.7)
IM ketamine	5 (19.2)	3 (11.5)	5 (19.2)	13 (50.0)	15 (57.7)	11 (42.3)	0 (0.0)

Data presented as n (%).

Discussion

Since different routes of drug administration may influence the sedative properties of drugs, this study was conducted to compare IN vs. IM ketamine in 2–6-year-old uncooperative children while receiving dental services. Various medications and methods have been tested to overcome a child's interfering behaviors in the dental office. Based on the results of this study, it can be stated that the IM administration of selected sedative agents, despite a child's resistance during injection, provides more efficient sedation according to the Houpt scale.

Intranasal ketamine has gained popularity due to the ease of administration, minimal distress, the reduced risk of needle-stick injuries, and the reduced need for skills to establish IV access.²⁰ Due to its acidic pH, ketamine may cause some discomfort, and the irritation and inflammation of the nasal mucosa, which may last for up to 1 h. In the current study, 2% lidocaine hydrochloride was instilled into the nasal cavities before the administration of ketamine to anesthetize the nasal mucosa, and thus reduce discomfort and irritation.²¹

The results of the current study demonstrated that the average onset time of the drug was 13 min for the IM route and 8 min for the IN route. When using the IN route, the drug directly enters the highly vascularized nasal mucosa and the systemic circulation. It appears that when the medication is administered IN, dropwise with a syringe, some of it enters the oropharyngeal area and is swallowed, so the amount of drug that is directly absorbed by the mucosa may be significantly reduced, resulting in a longer drug onset time in certain instances. Using the Mucosal Atomization Device (MAD®) for spraying the drug into the nasal mucosa significantly reduces the amount of drug entering the mouth, and accelerates the absorption and effect of the drug.^{22,23} Tsze et al. reported a sedation onset interval of 3–9 min with the nasal administration of 9 mg/kg of ketamine, using MAD.²⁴ In a study conducted by Shashikiran et al., the onset and recovery time of IN midazolam was reported to be shorter than in the case of the IM route.²⁵ Al-Rakaf et al. also reported the onset of sedation at about 8–15 min after the administration of IN midazolam,²⁶ which is less than the time recorded in the current study. In both of the abovementioned studies, midazolam was administered with a nasal atomizer.^{25,26} Before administering the drug into the nasal mucosa, the nose should be briefly examined for abnormalities and excessive nasal secretions, which may affect the amount of drug absorbed.²⁷

The results of this investigation demonstrated that out of 26 patients, only 9 children had sufficient sedation at 15 min and 30 min when using IN ketamine (Table 2). All the subjects receiving IM ketamine had their treatment completed in less than 30 min, which can be

justified by the fact that IM ketamine sedation has a more profound effect while in action. The droplet delivery of the medication to the nose may result in a speedy run into the oropharyngeal space before having a chance to be absorbed by the nasal mucosa, thus resulting in a lower uptake and a lesser effect of the drug. Therefore, the blood drug level and the level of sedation are directly affected if atomizers are not used.²⁸

Shashikiran et al. demonstrated that both IM and IN midazolam were successful, and stated that the same profile could be drawn for IM and IN midazolam in terms of effects and safety,²⁵ while Lam et al. claimed that the sedation induced by IM midazolam was deeper as compared to IN midazolam – children in the IM group showed less movement and better overall behavior according to the Houpt scale; however, no significant differences were reported with regard to children's crying during that investigation.²⁸

According to the results of this study, the parents believed that the IM route was more effective than the IN route. They were more satisfied with IM administration, even though the children showed less resistance to receiving the drug via the IN route. The parents expressed greater satisfaction with the time needed for their children to reach equilibrium for discharge for the IN route, as it was shorter than for the IM route. Of note, the swallowed amount of the drug which undergoes the first-pass metabolism can provide a prolonged effect in certain instances.¹⁷

Nausea and vomiting are the common side effects of ketamine, being more prevalent in adults in comparison with children.¹⁷ In the current study, vomiting and flushing were the 2 most common side effects reported by the parents after discharge. The incidence of vomiting was lesser than that of flushing, with no differences between the groups. An increased body temperature or flushing are the side effects of the atropine use, even at the minimum recommended dose of 0.02 mg/kg.¹⁷ The period of preoperative fasting and dehydration could also play a role in the incidence of flushing. Intravenous liquid was injected during the treatment to compensate. Excessive muscle contractions in the arms and legs were also observed in a few children in both groups as the side effects of ketamine. The concurrent use of benzodiazepines, such as midazolam, with ketamine, has been shown to be helpful in decreasing the incidence of these conditions.^{17,18}

There were no episodes of desaturation, behavioral disorders, hallucinations, or visual disturbances observed in children during this investigation. Diaz did not report any symptoms of nausea or vomiting after the administration of IN ketamine in comparison with placebo.²⁹ Bahetwar et al. stated that nausea and vomiting were noticed only in a small number of patients, while no statistically significant differences were reported between the groups.¹⁵

In the current study, the evaluation of physiological parameters (SpO₂, BP and RR) did not reveal any significant differences between the groups at different time intervals, which is consistent with previous studies.^{1,30}

Ketamine can cause BP to increase by about 20–25% above the pre-drug levels; therefore, it is recommended to use benzodiazepines along with ketamine to compensate for such a rise and an increased HR. It should be noted that ketamine can cause respiratory apnea at higher doses.¹⁷

An increase in HR was observed in both groups after the administration of local anesthesia. This increase may be due to the effects of ketamine or the epinephrine content in lidocaine. On the other hand, atropine, along with a sedative medication, can also play a role in increasing HR. Pain during the injection or dental treatment is also considered a contributing factor for an HR increase.

Conclusions

The IN route had a relatively acceptable sedation level for short treatment sessions (less than 10–15 min). The IM route provided more reliable sedation for treatment procedures longer than 10–15 min.

The parents preferred the IM route due to less discomfort of the patient.

In comparison with the IN route, IM drug administration is preferred in terms of inducing better sedation for the successful completion of treatment and causing the least amount of discomfort for the patient, as well as the stability of the cardiovascular and respiratory systems.

Ethics approval and consent to participate

Ethics approval was obtained from the Ethics Committee of the Dental Research Center at Shahid Beheshti University of Medical Sciences, Tehran, Iran (2013-7-ResCom-0011-approved). The parents of the children signed a written informed consent form.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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