Physiologic Effects of Intra-nasal Sedation with Midazolam and Ketamine in 3-6 Years old Uncooperative Children

[1]Majid Mehran [2]Sara Tavassoli-Hojjati [3]Nazila Ameli [*4]Mehdi Salehi Zeinabadi

[1]Assistant Professor, Dept. of Pediatric Dentistry, School of Dentistry, Shahed University, Tehran, Iran.
[2]Assistant Professor, Dept. of Pediatric Dentistry, School of Dentistry, Islamic Azad University, Tehran Branch, Tehran, Iran.
[3]Assistant Professor, Dept. of Orthodontics, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran.
[*4]Assistant Professor, Dept. of Pediatric Dentistry, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. E-mail: mehdi_s85@ymail.com

Abstract

Objective: Several medications have been used for sedation in children in dentistry and intra-nasal route has been reported to be an efficient way regarding patient cooperation. The aim of the present study was to compare the changes in physiologic parameters following intra-nasal midazolam and ketamine administration.

Methods: In this randomized cross-over double-blind trial, 17 uncooperative 3-6 years old children requiring at least two dental treatments were selected randomly and received intra-nasal ketamine (0.5 mg/kg) and midazolam (0.2 mg/kg) prior to the treatment using the other drug in the next visit. Physiologic parameters including blood pressure, heart rate, respiratory rate and O_2 saturation were measured and compared during the different time intervals using two way repeated measure ANOVA.

Results: The patients showed higher blood pressure and heart rate following ketamine administration compared to midazolam ($p<0.001$). No significant difference was found between the drugs at different time intervals regarding respiratory rate and O_2 saturation. ($p>0.05$)

Conclusion: In spite of significant differences between midazolam and ketamine regarding heart rate and blood pressure, both drugs can b e used as effective sedative medications without treatment interruption in children.

Key words: Cooperation, Intra-nasal, Ketamine, Midazolam, Physiologic parameters, Sedation.

Please cite this article as:

Mehran M, Tavassoli-Hojjati S, Ameli N, Salehi Zeinabadi M. Physiologic Effects of Intra-nasal Sedation with Midazolam and Ketamine in 3-6 Years old Uncooperative Children. J Dent Sch 2015;33(1):59-65.

Received: 14.05.2014 Final Revision: 07.06.2014 Accepted: 22.06.2014

Introduction:

According to common failures during dental treatments in children, utilization of a behavior control method including general anesthesia and conscious sedation is inevitable (1). Moreover, demands for sedation have been increased in recent years compared to general anesthesia (2). Different medications have been used as sedative agents in dentistry such as histamine, narcotics and benzodiazepine. Midazolam is a benzodiazepine with rapid onset and short duration. In anxious situations, it can effectively calm children (3, 4). Ketamine, with the suggested dose of 3mg/kg in combination with other sedative drugs and 6mg/kg in situ, is also useful in dental treatments (5, 6).

Several methods of drug administration like topical, intra-nasal, sublingual, rectal, intra and subcutaneous, intra-muscular, intra-pulmonary and inhalant have been introduced (4). Oral route is the most common way and has priority over other methods. In addition to its general acceptance, it is safe and inexpensive and its application is simple. On the other hand, young children do not accept it easily and its absorption

could be variable due to the presence of food, stomach autonomic tone, fear, emotional state, tiredness, drugs and stomach discharge intervals. Intra-nasal administration mostly is used in children in order to prevent oral or intra-venous routes. Intra-nasal drugs would be absorbed directly through vessels of nasal mucosa and do not enter the gastro-hepatic way. They have about the same onset of action as intra-venous administration with the plasma peak in about 10 minutes.

Parents/physician can drip the drug into the child nose with 1-3cc syringe without needle. Undiluted drug should be used in the nasal horn area to prevent its possible entrance to throat causing cough or sneeze (4).

It has been demonstrated that rectal or oral drug administration have longer onset of actions compared to intra-nasal way (7). Intra-nasal drug administration is non-invasive and requires less cooperation. Although, some authors believe that it is stressful and children acceptance is less. Also, nasal mucosal irritation and burning are of its shortcomings.

It has been reported that recovery after intra-nasal drug administration is faster than other methods although controversy exists (8). Moreover, variable results have been shown regarding physiologic parameter changes and even treatment interruption and O_2 prescription have been reported (8, 9).

So, the aim of the present study was to evaluate and compare the physiologic effects of intra-nasal midazolam and ketamine in uncooperative 3-6 years old children.

Methods:

Ethical approval was obtained from Ethics Committee of Shahed dental school. In this crossover double-blind study, 17 uncooperative 3-6 years old children meeting the inclusion criteria were selected. Informed consent was obtained and instructions were given to their parents. Parents informed that sedation procedure would be carried out by a specialist and a technician.

Selected children showed negative attitude according to Frankel category, at least one dentist had confirmed their noncooperation, were referred and also they required at least two identical dental treatments including pulpotomy and restoration/SS crown placement following local anesthesia.

Children with the history of allergy to sedative drugs, upper airway infection, nasal obstruction, limitation of neck movements, macroglossia, tonsillar hypertrophy, micrognathia and limitation in mouth opening were excluded.

Children were examined and a minimum of 6 hours of NPO (Nothing per Oris) for solids and 3 hours for liquid was suggested. No sign of fever, cough or sneezing should be observed during examination. Children were assigned to groups A and B, randomly. At first visit (after completion of questionnaire), a thorough history and demographic information with child's weight were obtained. Health status was determined and physiologicparameters including heart rate, respiratory rate, blood pressure and O_2 saturation recorded with pulse oxymeter (CHOICEMED, China) and pressure gauge (Mediasave, UK) as basic records.

After administration of 1cc lidocaine hydrochloride 2% (Pastur-Industrial Company of Iran) combined with 0.25 mg atropine (Aburaihan Industrial Company Tehran-Iran) in order to reduce tingle, each group received intra-nasal ketamine (Chemidaru Industrial Company Tehran-Iran) (0.5 mg/kg) and midazoalm (Chemidaru Industrial Company Tehran-Iran) (0.2 mg/kg) in two subsequent dental visits. The procedure was carried out with the presence of parents and in either upright or supine position according to patient cooperation. Each patient was used as his/her own control.

Physiologic parameters at first, before sedation (T0), during administration of anesthesia (10

minutes after administration of sedative agent) (T1), 5 and 15 minutes after local anesthesia administration (T2 and T3) and at the discharge time (T4) were recorded. At the end of treatment, children were transferred to recovery room and watched over to observe discharge criteria which were defined as follows:

1) Stable and acceptable heart function.
2) Normal breathing.
3) Normal response to stimulations and healthy protective reactions.
4) Ability to sit and talk.
5) Presence of child's caretaker.

Parents were questioned about the complications and their satisfaction 24 hours after discharge and the second dental visit was settled.

SPSS version 19 was used to analyze data. Mean and standard deviation (SD) at different time intervals evaluated using two-way repeated measure ANOVA. Data were suggested to be significant if P value was equal or less than 0.05.

Results:

17 children (9 males: 52.9% and 8 females: 47.1%) with the mean age of 4.5 (0.9) and ASA I physical status were studied. The mean weight of children was 16.2 (3.6) kg with the range of 24 (10.5) kg. The reason of sedation in 15 children was fear and anxiety and in other two was under development and young age.

Table 1 shows the mean and SD of four physiologic parameters.

Table 1- Mean and standard deviation of physiologic parameters following sedation with ketamine and midazolam

Time	Medication	mean	SD	mean	SD	mean	SD	mean	SD
		Heart rate		Oxygen saturation		Respiratory rate		Blood pressure	
Before drug administration	Ketamine	123.5	12.7	97.0	0.007	25.1	1.8	109.9	4.3
	Midazolam	124.3	11.7	97.0	0.009	24.9	2.2	110.6	5.2
At local anesthesia administration	Ketamine	130.5	12.8	97.0	0.006	24.1	2.0	117.6	4.7
	Midazolam	126.3	12.4	97.0	0.006	24.5	2.1	113.3	5.3
5th minute	Ketamine	130.5	12.4	97.0	0.006	24.4	1.8	120.1	4.4
	Midazolam	125.1	12.7	95.0	0.07	24.4	2.0	113.7	4.9
15th minute	Ketamine	128.6	13.2	97.0	0.006	24.6	1.9	118.7	5.1
	Midazolam	125.6	13.5	97.0	0.008	24.8	1.6	112.5	6.3
Discharge time	Ketamine	126.4	12.0	97.0	0.008	24.8	1.9	116.0	5.6
	Midazolam	123.3	13.6	97.0	0.007	24.3	1.8	110.7	6.8

According to Diagram 1, heart rate differences following ketamine administration between T0 and T1 are almost the same and shows significant difference compared to three other time points. (T2, T3 and T4) (p<0.05).

Diagrams 2 and 3 reveal that changes in O_2 saturation and respiratory rate were not significantly different between two drugs and at different time intervals, respectively (p>0.05).

Increase in blood pressure following ketamine administration was significantly higher compared to midazolam. (Diagram 4) Moreover, blood pressure changes at different time intervals were significantly higher than that of ketamine administration (p<0.05), while midazolam resulted in significant difference in blood pressure only at T2 (p<0.05). It means that the most increase in blood pressure happens 5 minutes after local anesthesia administration using midazolam.

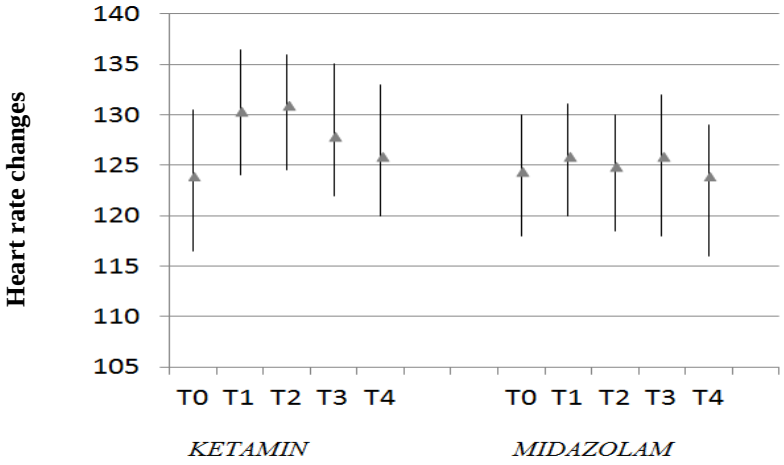

Diagram 1- Heart rate changes following intra-nasal sedation with ketamine and midazolam at different time intervals

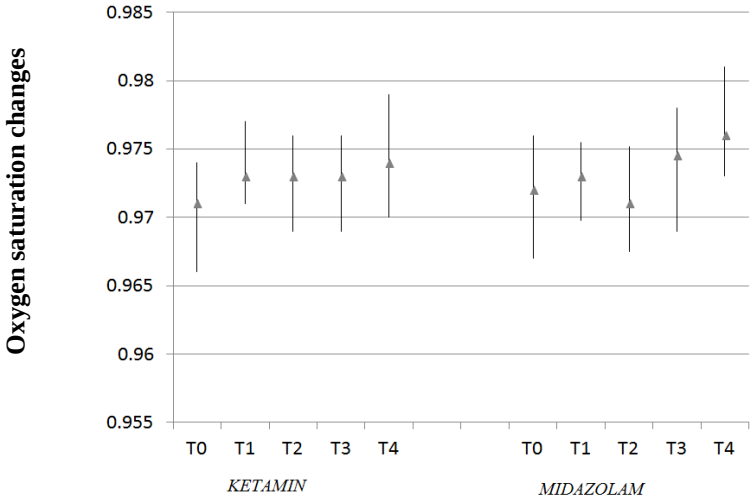

Diagram 2- Oxygen saturation changes following intra-nasal sedation with ketamine and midazolam at different time intervals

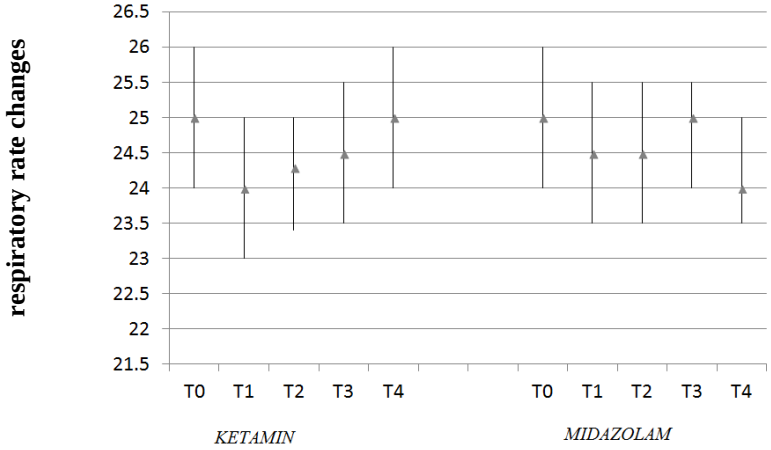

Diagram 3- Respiratory rate changes following intra-nasal sedation with ketamine and midazolam at different time intervals

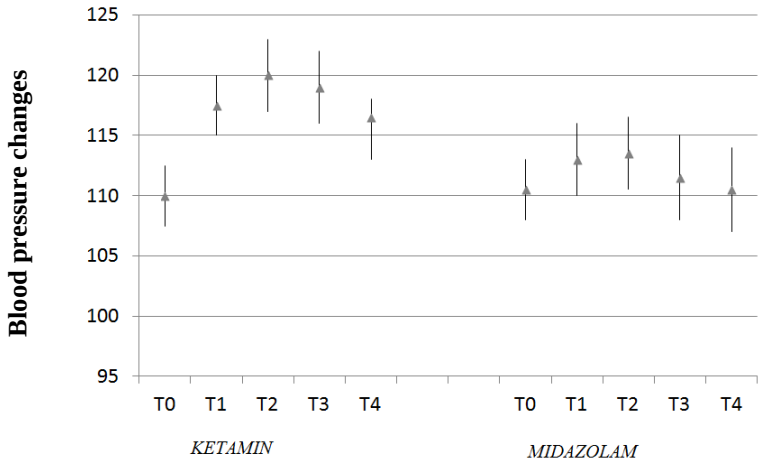

Diagram 4- Blood pressure changes following intra-nasal sedation with ketamine and midazolam at different time intervals

Discussion:

It is well-known that sedative agents would be helpful in behavior control and ease of dental operation in children. (10, 11) In the present study, we compared the effects of intra-nasal midazolam and ketamine on physiologic parameters of 3-6 years old uncooperative children.

The results show that differences in heart rate before drug administration were not significant while during local anesthesia administration, 5 and 15 minutes after anesthesia administration and at the discharge time, the mean heart rate following ketamine use was significantly higher than midazolam. On the other hand, the mean blood pressure found to be significantly higher at local anesthesia administration, 5 and 15 minutes after anesthesia administration following ketamine compared to midazolam. No significant differences observed regarding O2 saturation and respiratory rate between two medications at different time intervals.

Researches on the conscious sedation using ketamine and midazolam have demonstrated the increase in heart rate subsequent to their administration (12, 13). It is obvious that children would experience the increases in heart rate, partly due to the stressful situation during dental treatment (12). Ketamine could result in slow increase in heart rate and blood pressure which has little clinical effects (13, 14).

Golpayegani, *et al*. (2012) compared the combination of oral midazolam-ketamine with midazolam-prometazine in 2-6 years old children and reported that after 30 minutes, the heart rate increased significantly following ketamine administration (p=0.03) (15).

Consistently, Lotfy, *et al*. (1970) stated that increase in arterial blood pressure and heart rate is the definite and usual effects of ketamine in children which implies the stimulation of sympathic system (16).

Tobias and Leder (2011) demonstrated that ketamine has limited effects on respiratory system while it results in dose-dependent increase in heart rate and blood pressure due to sympatethic stimulation and release of endogenous catecholamines. Also, they reported that increase in blood pressure and tachycardia following its administration, could be decreased by combining the drug with barbiturates or benzodiazepine (17).

Wilton, *et al*. (1988) compared 0.3 mg/kg and 0.2 mg/kg intra-nasal midazolam in 1.5-5 years old children and found no difference in O_2 saturation or respiratory rate. They concluded that 0.2 mg/kg intra-nasal midazolam would

result in adequate sedation in pre-school children (18).

Weldon, *et al*. (1992) also reported that no significant difference was observed in heart rate, respiratory rate or hemoglobin O2 saturation following Atropine or midazolam in children (19).

Conversely, Tanaka, *et al*. (2000) found no significant difference in heart rate and blood pressure changes between rectal administration of ketamine and midazolam. This can be explained by greater and faster drug absorption by through intra-nasal administration compared to rectal route (20).

Also, von Ungern-Sternberg, *et al*. (2009) stated that oral midazolam in children whit healthy respiratory system, would result in slight changes in respiratory variables for short duration and the caregiver should notice that drug administration in children with impaired respiratory function leads to greater functional deficiency (21).

Tavassoli-Hojjati, *et al*. (2014) demonstrated that oral and buccal administration of midazolam does not result in significant changes in physiologic parameters after 10, 20 and 30 minutes (22).

Intra-nasal drug administration is reported to produce more effective and rapid sedation due to direct drug absorption, better biologic access and obtaining faster plasma peak. Moreover, according to rapid drug excretion, sedative effect would decrease at the end of treatment. Vomiting is one of the common complications after intra-nasal ketamine administration (35.3%) which could be related to swallowed drug. This complication is temporary and has been mentioned in previous studies (23).

Conclusion:

Changes in O_2 saturation and respiratory rate showed no significant differences between intra-nasal ketamine and midazolam and at different time intervals. In spite of significant increase in heart rate and blood pressure following ketamine administration, there is no need to interrupt treatment procedure and both drugs induce adequate sedation in children.

Conflict of Interest: "None Declared"

References:

1. Lökken P, Bakstad OJ, Fonnelöp E. Skogedal N, Hellsten K, Bjerkelund CE, *et al* . Conscious sedation by rectal administration of midazolam or midazolam plus Ketamine as alternatives to general anesthesia for dental treatment of uncooperative children. Scand J Dent Res 1994;102: 274-280.
2. Roelofse JA. What's new in paediatric conscious sedation in dentistry? SAAD Dig 2010; 26: 3-7.
3. Nathan JE, Vargas KG. Oral midazolam with and without meperidine for management of the difficult young pediatric dental patient: a retrospective study. Pediatr Dent 2002; 24: 129-138.
4. Malamed SF. Sedation: A guide to patient management. 4th Ed. London: St.Louis: The C.V. Mosby Co. 2002; Chap10: 22-31, 187-195.
5. Moore PA. Administering sedation: the controversy continues. Gen Dent 2007; 55: 273-274.
6. Yamada CJ. New challenges in management of the anxious pediatric dental patient. Hawaii Dent J 2006; 37: 14-16.
7. Lee-Kim SJ, Fadavi S, Punwani I, Koerber a. Nasal versus oral midazolam sedation for pediatric dental patient. J Dent Child (Chic) 2004; 71: 2, 126-130.
8. Primosch RE, Guelmann M. Comparison of drops versus spray administration of intranasal

midazolam in two-and three-year-old children for dental sedation. Pediatr Dent 2005; 27: 401-408.
9. Roelofse JA, Roelofse PG. Oxygen desaturation in a child receiving a combination of ketamine and midazolam for dental extractions. Anesth Prog 1997; 44: 68-70.
10. Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, *et al*. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Ann Emerg Med 1998; 31: 688-697.
11. Brosius KK, Bannister CF. Midazolam premedication in children: a comparison of two oral dosage formulations on sedation score and plasma midazolam levels. Anesth Analg 2003; 96: 392-395.
12. Lima AR, da Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. Pesqui Odontol Bras 2003; 17: 206-211.
13. Roelofse JA, Joubert JJ, Roelofse PG. A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of pediatric dental patients. J Oral Maxillofac Surg 1996; 54: 838–844.
14. Casamassimo PS, Fields HW, McTigue D, Nowak AJ. Pediatric dentistry, infancy through adolescence. 5th Ed. Elsevier: W.B. Saunders Co. 2013; Chap 8: 116.
15. Golpayegani MV, Dehghan F, Ansari G, Shayeghi S. Comparison of Midazolam-Ketamine and Midazolam-Promethazine as sedative agents in pediatric dentistry. Dent Res J (Isfahan) 2012; 9: 36-40.
16. Lotfy AO, Amir-Jahed AK, Moarefi P. Anesthesia with ketamine: indications, advantages and shortcomings. Anesth Analg 1970; 49: 969-974.
17. Tobias JD, Leder M. Procedural sedation: A review of sedative agents, monitoring and management of complications. Saudi J Anesth 2011; 5: 395-410.
18. Wilton NC, Leigh J,Rosen DR, Pndit UA. Preanesthetic sedation of preschool children using interanasal midazolam. Anesthesiology 1988; 69: 972-975.
19. Weldon BC, Watcha MF, White PF. Oral midazolam in children: effect of time and adjunctive therapy. Anesth Analg 1992; 75: 51-55.
20. Tanaka M, Sato M, Saito A, Nishikawa T. Reevaluation of rectal ketamine premedication in children, comparison with rectal midazolam. Anesthesiology 2000; 93: 1217-1224.
21. von Ungern-Sternberg BS, Erb TO, Habre W, Sly PD, Hantos Z. The impact of oral premedication with midazolam on respiratory function in children. Anesth Analg 2009; 108: 1771-1776.
22. Tavassoli-Hojjati S, Mehran M, Haghgoo R, Tohid-Rahbari M, Ahmadi R. Comparison of oral and buccal midazolam for pediatric dental sedation: A randomized, cross-over, clinical trial for efficacy, acceptance and safety. Iran J Pediatr 2014; 24: 198-206.
23. Holloway VJ, Husain HM, Saetta JP, Gautam V. Accident and emergency department led implementation of ketamine sedation in paediatric practice and parental response. J Accid Emerg Med 2000; 17: 25-28.