A Comparative Evaluation of Drops versus Atomized Administration of Intranasal Ketamine for the Procedural Sedation of Young Uncooperative Pediatric Dental Patients: A Prospective Crossover Trial

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Objective: *The objective of this study was to compare and evaluate the efficacy and safety of drops and atomized administration of intranasal ketamine (INK) in terms of behavioral response for agent acceptance during administration and for agent efficacy and safety for the sedation of young uncooperative pediatric dental patients.* ***Study design:*** *Thirty Four uncooperative ASA grade-1 children, requiring dental treatment were randomly assigned to receive INK as drops and atomized spray in one of the subsequent visit. This was a two stage cross-over trial and each child received INK by both modes of administration. The vital signs were monitored continuously during each visit.* ***Results:*** *A statistically significant difference in patients acceptance ($P<0.0001$) was observed in the atomized administration when compared to drops administration for the procedural event of drug administration. Moreover, there were also significant differences ($P<0.05$) between onset of sedation and recovery time between two groups. All the vital signs were within normal physiological limits and there were no significant adverse effects in either group.* ***Conclusions:*** *INK is safe and effective by either mode of intranasal (IN) drug administration for moderate sedation in facilitating dental care for anxious and uncooperative pediatric dental patients. Moreover, INK when administered with the mucosal atomization device, the acceptance of the drug was associated with less aversive reaction, rapid onset and recovery of sedation, as compared to the drop administration of the same agent.*

Keywords: *Moderate sedation, intranasal ketamine, intranasal drops and spray.*
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INTRODUCTION

The management of pain, anxiety and unwanted mobility in children undergoing various procedures, or procedural sedation and analgesia (PSA), has developed considerably during recent years[1,2] and has substantially reduced the need of general anesthesia in both medical and dental practice.[3] Moreover, researchers have concluded that PSA can be safely administered by non-anesthesiologists outside the operating room[4] in which dental offices have been recognized as potential areas.[5,6]

A number of drugs and various routes of administration (oral, submucosal, transmucosal, intramuscular, intravenous, rectal, etc.) have been used to this end for PSA in dental office, but each of the above routes has its own advantages and disadvantages. Recently, the IN route has gained momentum in the field of pediatric dental sedation due to its several significant advantages over other routes.[7,8,9] Hence, a variety of sedative and analgesics including ketamine (K) have been tried intransally for the procedural sedation of young, uncooperative pediatric dental patients. However, various authors have reported that the mode (drop and spray) of IN administration of drugs affects the efficacy.[10,11] Thus, the present prospective crossover clinical trial was undertaken to compare and evaluate the efficacy and safety of ketamine when administered intranasally as a drop and atomized spray for sedation of young uncooperative pediatric dental patients.

METHOD

Thirty four healthy children (ASA type I) between the ages of 2-6 years for whom basic behavior modification technique were not successful in providing dental treatment

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Table 1. Behavior/Response to treatment (ease of treatment completion) rating scale

SCORE	CLASSIFICATION	BEHAVIORAL SIGN
5	EXCELLENT	Quiet and cooperative, treatment completed without difficulty
4	GOOD	Mild objections or whimpering but treatment not interrupted. Treatment completed without difficulty
3	FAIR	Crying with minimal disruption to treatment. Treatment completed with minimal difficulty
2	POOR	Struggling that interfered with operative procedures. Treatment completed with difficulty
1	PROHIBITIVE	Active resistance and crying, treatment cannot be rendered

'*Satisfactory' session*- response to treatment rating score of '4' or '5' through the first 30 minutes of the session
'*Unsatisfactory' session*- score less than '4' or '5' even in one reading during the first 30 minutes of the session

(Table 1)[6] and whose treatment necessitated the administration of local anesthetic injection were recruited into the study which was approved by Institutional Ethics Committee, Research Cell, CSM Medical University, Lucknow, India. Risk and benefits of the sedation followed by the pre-sedation instructions were explained to the parent/guardian at the initial examination appointment. Each parent/guardian was requested to fill a written consent form at the initial appointment. The inclusion criteria also required that they had no known hypersensitivity to K or any other medication likely to interfere with the study drug. A comprehensive pre-anesthetic assessment (including tonsil and adenoid assessment, mouth breathing, speech, hypo-nasality, snoring, airway and chest examination) were performed by a Professor of the Department of Anesthesiology, CSM Medical University, Lucknow, India.

This study was envisaged to compare and evaluate the efficacy and safety of K as drops and atomized spray given by IN route for sedation in pediatric dental patients while delivering dental treatment to uncooperative children. All the enrolled patients were given K (6mg/Kg) by both the modes (drops and atomized spray) on two different visits in a crossover manner. During each sedation session the children were evaluated for the behavior response during the administration of drug while after the administration of drugs, they were evaluated for the time of onset, depth of sedation, behavioral response during dental treatment, changes in vital signs, the oxygen saturation levels, adverse effects during and after the sedation sessions, recovery times and the overall success with sedation. However, rate of success of sedation with each regimen was the main outcome measured.

To deliver drugs by IN route, the quantity of drugs should be kept minimum. Hence, concentrated solution of the drug was used. K was not available in concentrated form hence it was manufactured by Kwality Pharmaceutical Ltd in the concentration of 100mg/ml on a special request to the company, for the purpose of this study. It was a crossover trial so all the patients received K through IN route by both modes-drops and atomized spray. The order in which they were administered was generated using an online randomization generator.

On the day of dental treatment, to obtain assurance of the children's health they were re- evaluated by an anesthesiologist who was present throughout the procedure. The vital signs and the peripheral oxygen saturation levels were examined and recorded. All the dental procedures were carried out by the author himself. The treatment procedures for each patient were standardized in such a way that similar procedures were performed on both the visits. Half volume of the drug was administered into each nostril with the child in semi recumbent position or in parent's lap using an insulin injection syringe without needle for drop method while mucosal atomizer device (MAD100, Mucosal Atomizer Devise; Wolf Tory Medical, Inc Salt Lake City, UT) (Fig. 1) for atomized method. The child's behavior during IN drug administration, as well as any possible complication includ-

Figure 1. MAD 100 Mucosal Atomizer (Wolfe Tory Medical, Salt Lake City Utah)

ing burning sensation, coughing, sneezing, etc were carefully assessed and recorded. After the onset of sedations the vital signs i.e. pulse rate, blood pressure, respiratory rate and the oxygen saturation were recorded at regular interval of 5 minutes. All patients received injection of local anesthesia (2% lignocaine with 1:200000 adrenaline) either in the form of nerve block or infiltrated locally. If the child became uncooperative during the treatment procedure physical restraints were applied by the dental assistant that includes mouth prop, papoose board, manual hold or the combination of the above. The use of physical restraints during the treatment procedure was documented. The presences of any side effects or complications (Eg.vomiting, coughing, sneezing, etc) were also recorded.

The Ohio State Behavioral Rating Scale (OSBRS) (Table 2), as described by Lochary and co-workers[12] was employed for the patient's acceptance of drug administration. The OSBRS uses a hierarchical scale labeled for observed behavior as: (1) quit; (2) crying; (3) struggling; and (4) crying/struggling. The lowest OSBRS (most aversive behavior displayed) was recorded for the procedural event of drug administration.

The ease with which treatment could be completed and the level of sedation were measured using separate 5 point scales that was used in previous study conducted in the same centre[6] (Table 1 and 3). (Basically this rating scale is a modified from AAPD sedation record in our institution). The above ratings were recorded at a regular interval of 5 minutes. Calibration involved rating of recorded videographic segment of the sedation sessions conducted in this centre, previously rated by a Professor in the Department of Pediatric Dentistry who was involved in this study and two other studies conducted in the same centre.[6,13,14,15]

Table 2. Ohio State Behavioral Rating Scale (OSBRS) for patient's acceptance of the drug during administration

1	Crying and struggling (CS)
2	Struggling (S)
3	Crying (C)
4	Quiet (Q)

Table 3. Sedation rating scale

1	NO SEDATION	Typical response /cooperation for this patient
2	MINIMAL	Anxiolysis
3	MODERATE	Purposeful response to verbal commands
4	DEEP	Purposeful response after repeated verbal command or painful stimulation.
5	GENERAL ANESTHESIA	Not arousable

'*Adequate' sedation*- sedation rating score of '2' or '3' through the first 30 minutes of the session
'*Inadequate' sedation*- score other than '2' or'3' even in one reading through the first 30 minutes of the session

After the completion of the treatment, patient was transferred in a quiet room for recovery. Once fully recovered, the time required for complete recovery was recorded. The vital signs were re-evaluated and the patient was discharged, when the AAPD sedation guidelines for discharge were met[16] and an Aldrette score[17] of 9 or greater was achieved. The parent/guardian accompanying the child patient was provided postoperative instructions and the emergency telephone number and were contacted next day and enquired for the presence of any adverse reactions.

The sedation session (treatment outcome) was considered safe and 'successful' if: (1) response to treatment score of '4' or '5' (satisfactory) and sedation score of '2' or '3' (adequate sedation) was obtained throughout the treatment, (2) physiological parameter remained within 20% of baselines values, (3) oxygen saturations remained at 90% or greater, (4) physical restraints were not used during the dental procedure and (5) no major side effects were observed during and after sedation sessions.

Statistical analysis

The effect of K on vital signs, oxygen saturation, onset time of sedation and recovery time were compared by Wilcoxon matched pairs test. The difference in the depth of sedation, response/behavior during treatment and treatment outcome between the two groups were analyzed by Fisher's exact test as the response variables for all these parameters had only two possible outcomes (adequate/inadequate; satisfactory/unsatisfactory and successful/unsuccessful. Patient's acceptance of drug administration was compared with χ^2 test. A two-tailed (α=2) probability (p) value less than 0.05 ($p<0.05$) was considered to be statistically significant. All analyses were performed on SPSS (version 15.0).

RESULTS

Total 34 children were enrolled (16 female and 18 male) for this study who were treated with K by both the modes in two separate visit in cross over fashion, thus, a total of 68 sedation sessions were performed. The age of all subjects ranged from 2-6 yrs with mean (± SD) of 4.44 ± 1.65 yrs and mean (± SD) weight of 13.88 ± 4.26 kg. The results obtained have been summarized in Table 4.

There was significant difference ($p< 0.05$) in the duration required for the onset of sedation between the two groups. When K was administered as atomized spray, the onset of action was faster with a mean duration of 5.13 minutes, while K had a slower onset with a mean duration of 5.79 minutes when administered with drops. Similarly, there was significant differences in the duration required for the recovery also. The mean recovery time in children sedated with drops was found to be significantly ($p<0.05$) longer as compared to children sedated with atomizer. Thus, children recovered faster when sedated with atomized K and slower when sedated with drops K. Atomized K provided 'adequate' depth of sedation during maximum number of

Table 4: Primary outcome measures of patients treated with two different groups

Parameter		Spray	Drops	'p' value
Onset of sedation (min) n=34*	Mean Range	5.13±1.21 (4 – 8)	5.79±1.42 (5 – 8)	0.0431 Wilcoxon matched pairs test
Adequate depth of sedation (n%)		33(97.05%)	31(91.17%)	0.6135 Fisher' exact test
Ease of treatment completion 'satisfactory' session (n%)		32(94.11%)	30(88.23%)	0.6728 Fisher' exact test
Recovery time (min)	Mean Range	38.36±3.29 (32 – 44)	39.98±3.18 (34 – 46)	0.0429 Wilcoxon matched pairs test
	Number of sessions$	33	31	
Acceptance of drug administration	Poor Fair Good Excellent	2(5.9%) 2(5.9%) 6(17.6%) 24(70%)	15(44.1%) 8(23.5%) 3(8.85) 8(23.5%)	0.0001 χ^2 test
Treatment outcome 'successful' session (n%)		32(94.11%)	29(85.29%)	0.4275 Fisher' exact test
'Unsuccessful' session (n%)	Session completed with PR Aborted session	1(2.94%) 1(2.94%)	3(8.82.%) 2(5.88%)	

* n = 34, implies the number of sessions; $ recovery time calculated only from those children who were 'adequately' sedated throughout the session.

sedation sessions (97.05%) and provided 'satisfactory' completion of treatment during 32 sedation session.

For the procedural event of the drug administration, the atomized group demonstrated a statistically significant reduction (P<0.0001) in aversive behaviors compared to drop administration when measured by the OSBRS. Thus, in this group acceptance of drug was better as compared to the group in which K was given by drop mode.

Wilcoxon matched pairs test was applied to evaluate the differences in means among each of the sets of the vital signs and oxygen saturation level recorded during each visit. The relative changes in the vital signs observed during treatment were statistically not significant on inter-group comparison. Those were within 20% of baseline values and hence the changes observed were considered clinically insignificant. Moreover, the oxygen saturation values remained above 90% during each sedation session.

Vomiting was the only adverse effect observed on four occasions with drops and twice with spray administration. It occurred after the completion of treatment session, thus, did not affect the delivery of the treatment.

The overall success rate (treatment outcome), was more successful with atomized K (94.11%) when compared to the drops K (85.29%). Thus, in the present study, the overall success rate of atomized INK was higher as compared to drops INK though this difference was not significant statistically.

DISCUSSION

Providing comprehensive oral care to fearful, uncooperative and uncontrollable pediatric dental patients can be unpleasant for all parties involved. Despite the dentist's best effort to employ conventional technique, the behavioral management of challenging pediatric dental patients often requires preoperative pharmacological intervention for delivering dental care. Although, the practice of pediatric dentistry has changed considerably over the past several decades, the apprehension and fear of any procedure is still persisting in the child patient, thus, further advancement in both better drugs and technique might bring improvement in better behavior of the patients.

K, which has been in use since 1970, is often referred to as a dissociative agent causing a functional and electrophysiologic dissociation between the thalamoneocortical and limbic areas of the brain[18,19] leading to "a trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respiration, and cardiopulmonary stability."[20] It is particularly well suited to pediatric procedures and provides better sedation with fewer respiratory complications than midazolam/fentanyl[21,22] making a quite ideal agent for pediatric dental sedation. Moreover, several large studies document that it has a wide margin of safety.[19,23-27] However, it has been used by few researchers for pediatric dental sedation, and hence, K was chosen for our study.

A survey of US advanced education programs in pediatric dentistry reported a rise in the use of IN administration of sedatives[28] for the sedation of young, uncooperative pediatric dental patients. IN drugs have been deployed primarily in pediatric patients as a means of circumventing the need for injection or bitter tasting oral drugs in children[29] especially in unwilling patients.[7,8] Since, a simple and non invasive technique, IN administration has none of any potential side effects and complications such as inadvertent intravenous or arterial injection, nerve injury and infection associated with intramuscular injection.[30] Moreover, absorption

of IN drugs occurs directly into the central circulation, bypassing the entero-hepatic circulation.[31]

Various studies[32-37] of IN administration of sedative especially midazolam have been reported in the literature in the field of pediatric dentistry. Though, clinical trials of INK are well documented in medicine[38-40] its use in pediatric dentistry is not significantly reported. However, oral K has been used by various authors[41-46] and they have reported promising results. Previously, various authors have used drops for the IN sedation of uncooperative pediatric dental patients with midazolam[7,8,9,32-36] and K[15] but more recently use of an atomizer for intranasal administration has become more popular.[47-50] Various authors[37,47] have reported improved patients tolerance to spray administration using an atomizer over using drops. Hence, this study was undertaken to compare and evaluate the efficacy and safety of INK as drops and spray for the procedural sedation of young, uncooperative pediatric dental patients as a behavior management technique for providing comprehensive oral care to these patients.

Result of our study indicated that, although the INK when administered as drops or atomized both are safe and effective for providing PSA in pediatric dental patient, there are significant difference in patient acceptance, onset of sedation and recovery time between these two modes of administration. INK when administered through MAD provided better patient acceptance with rapid onset and recovery of sedation with higher overall success rate.

Emergency reactions are well established such as the adverse effects of K; however these were not detected in any of our patients. Other workers also did not detect emergence reactions among child patients receiving either low dose intramuscular or oral K for pre-anesthetic sedation.[39,51] Moreover, one study has demonstrated that the incidence of emergence reactions in children is lower than in adults patients, varying from 0 to 5% in the former, to > 30% in the later.[52] In our study vomiting was the only adverse effect reported. It was observed on four occasions with drops and twice with spray administration. It is worthwhile to note that in all the cases vomiting occurred after the completion of treatment session, thus, it did not adversely affect the delivery of the treatment. Moreover, a detail enquiry from the parents revealed that these children had not followed the pre-procedural instruction regarding meal. Thus, the vomiting might be associated with the food consumed by the child patient before coming for the dental treatment.

For a pediatric dentist to perform a dental procedure successfully, three aspects in respect of PSA in dental office are crucial i.e onset, depth and recovery of sedation. An ideal agent and route would be which has quick onset of action, provides adequate depth of sedation and rapid recovery of sedation avoiding unnecessary stay of the child in the dental clinic. The findings of present study using a new commercially available atomizer (MAD) showed rapid onset and recovery of sedation, adequate depth and overall success rate of sedation in addition to the better patient tolerance in larger number of patients as compared to the IN drops mode of administration. This makes atomized spray of INK, a quite ideal agent for PSA for management of young uncooperative pediatric dental patients in dental office.

CONCLUSION

Based on this study it can be concluded that INK with either mode of administration provides good sedation and represents a safe and effective pharmacological technique for procedural sedation of young, uncooperative pediatric dental patients. However, use of MAD for the administration of INK provides better patient acceptance, rapid onset and recovery of sedation and higher overall success rate for procedural sedation in such patients.

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REFERENCES

1. Krauss B, editor. Pediatric procedural sedation and analgesia. Philadelphia: Lippincott Williams and Wilkins; 1999.
2. Krauss B, Green S. Sedation and analgesia for procedures in children. N Engl J Med, 342: 938–45, 2000.
3. Kaplan RF, Yang CI. Sedation and analgesia in pediatric patients for procedures outside the operating room. Anesthesiol Clin North America, 20(1): 181–94, 2002.
4. Pitetti RD, Singh S, Pierce MC. Safe and efficacious use of procedural sedation and analgesia by non-anesthesiologists in a pediatric emergency department. Arch Pediatr Adolesc Med, 157(11): 1090–6, 2003.
5. Doyle L, Colletti JE. Pediatric procedural sedation and analgesia. Pediatr Clin North Am, 53(2): 279–92, 2006.
6. Padmanabhan MN, Pande RK, Saksena AK, Chandra G. A comparative evaluation of agents producing Analgo-sedation in pediatric dental patients. Journal of Clinical Pediatric Dentistry, 34(2): 183–189, 2009.
7. Wilton NC, Leigh J, Rosen DR, Pandit UA. Pre-anesthetic sedation of preschool children using intranasal midazolam, Anesthesiology, 69: 972–975, 1988.
8. Saint–Maurice C, Landias A, Delleur MM, Esteve C, MacGee K, Murat I. The use of midazolam in diagnostic and short surgical procedures in children. Acta Anesthesiol Scand Suppl, 92: 39, 1990.
9. Lee-Kim SJ, Fadavi S, Punwani I, Koerber A. Nasal Versus oral midazolam sedation for pediatric dental patients. J dent child (chic), May-Aug, 71(2): 135–138, 2004.
10. Henry RJ, Ruano N, Casto D, Wolf RH. A pharmacokinetic study of midazolam in dogs: nasal drop vs. atomizer administration. Pediatr Dent, 20: 321–6, 1998.
11. Timothi R. Wolfe and Tony B. Intranasal drug delivery: An Alternative to Intravenous Administration in Selected Emergency Cases. Journal of Emergency Nursing, April 30: 2: 141–47, 2004
12. Lochary ME, Wilson S, Griffen AL, et al. Temperament as a predictor of behavior for conscious sedation in dentistry. Pediatr Dent, 15: 348–352, 1993.
13. Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedative as premedication in pediatric dentistry. J Clin Pediatr Dent, 26(2): 161–164, 2002.

14. Koirala B, Pandey RK, Saksena AK, Kumar R, Sharma S. A comparative evaluation of newer sedatives in conscious sedation. Journal of Clinical Pediatric Dentistry, 30: 273–276, 2006.
15. Bahetwar SK, Pandey RK, Saksena AK, Chandra G. A comparative evaluation of intranasal midazolam, ketamine and their combination for sedation of young uncooperative pediatric dental patients: a triple blind randomized crossover trial. Accepted for publication. Journal of Clinical Pediatric Dentistry, 2011
16. American Academy of Pediatrics; American Academy of Pediatric Dentistry, Coté CJ. Wilson S. Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatr, Jan 118(6): 2587–602, 2006.
17. Citerio G, Franzosi MG, Latini R. Anaesthesiological strategies in elective craniotomy: randomized, equivalence, open trial- the NeuroMorfeo trial. Trials, Apr10: 19, 2009.
18. McCarty EC, Mencio GA, Walker LA, Green NE. Ketamine sedation for the reduction of children's fractures in the emergency department. J Bone Joint Surg Am, 82-A: 912–18, 2000.
19. Reich DL, Silvay G. Ketamine on the first twenty five years of clinical experience. Can J Anaesth, 36: 186–97, 1989.
20. Green SM, Krauss B. The semantics of ketamine. Ann Emerg Med, 36: 480–2, 2000.
21. Kennedy RM, porter FL, Miller JP et al. Comparison of fentanyl/midazolam with ketamine /midazolam for pediatric orthopedic emergencies. Pediatrics, 102: 956–63, 1998.
22. McGlone R, Fleet T, Durham S, Hollis S. A comparison of intramuscular ketamine with high dose intramuscular midazolam with and without intranasal flumazenil in children before suturing. Emerg Med J, 18: 34–8, 2001.
23. Green SM, Rothrock SG, Lynch EL et al. Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile in 1022 cases. Ann Emerg Med, 31: 688–97, 1998.
24. Dachs RJ, Innes GM. Intravenous ketamine sedation of pediatric patients in the emergency department. Ann Emerg Med, 29: 146–50, 1997.
25. Green SM, Clark R, Hostetler MA et al. Inadvertent Ketamine overdose in children; Clinical menifestations and outcome. Ann Emerg Med, 34: 492–7, 1999.
26. Holloway VJ, Husain HM, Saetta JP, Gautam V. Accident and emergency department led implementation of ketamine sedation in pediatric practice and parental response. J Accid Emerg Med, 17: 25–8, 2000.
27. Priestley SJ, Taylor J, McAdam CM, Francis P. Ketamine sedation for children in the emergency department. Emerg Med, 13: 82–90, 2001.
28. Wilson S, Farrell K, griffen A, et al. Conscious sedation experiences in graduate pediatric dentistry programs. Pediatr Dent, 23: 307–14, 2001.
29. Kain ZN, Mayes LC. Anxiety in children during the peri-operative period. In Bamstein M, Gennevro J (eds): Child Development and Behavioral Pediatrics. Mahwah NJ, Lawrence Erlbaum Associates, 85–103, 1996.
30. Hanson DJ. Intramuscular injection: Injuries and complications. Gen Pract, 27: 109–12, 1963.
31. Sarkar MA. Drug metabolism in the nasal mucosa. Pharmaceutic Res, 9: 1–3, 1992.
32. Al-Rakaf H, Bello LL, Turkustani A, Adenubi JO. Intranasal midazolam in conscious sedation of young paediatric dental patients. Int J Paediatr Dent, 11(1): 33–40, 2001.
33. Mazaheri R, Eshghi A, Bashardoost N, Kavyani N. Assessment of intranasal midazolam administration with a dose of 0.5 mg/kg in behavior management of uncooperative children. J Clin Pediatr Dent, 32(2): 95–99, 2007.
34. Fukata O, Braham RL, Yanase H, Kurosu K. The sedative effect of intranasal midazolam administration in the dental treatment of patients with mental disabilities. Part 2: optimal concentration of intranasal midazolam. J Clin Pediatr Dent, 18(4): 259–65, 1994.
35. Fuks A., Kaufman E., Ram D., Hovav S. Shapira J. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patient. Pediatr Dent, 16: 301, 1994.
36. Roelofse JA, Shipton EA, De La Harpe CJ, Blignaut RJ. Intranasal sufentanil / Midazolam Versus Ketamine/Midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: A prospective, double-blind, randomized comparison. Anesth Prog, 51: 114–121, 2004.
37. Primosch RE, Guelmann Marcio. Comparison of Drops Versus Spray Administration of Intranasal Midazolam in Two-and Three-year old Children for Dental Sedation. Pediatr Dent, 27:5: 401–8, 2005.
38. Gharde P, Chauhan S, Kiran U. Evaluation of Efficacy of intranasal Midazolam, Ketamine and their Mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. Ann Card Anaesth, 9: 25–30, 2006.
39. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. Anesthesiology, 76: 28–33, 1992.
40. Roelofse JA. The evolution of ketamine applications in children. Pediatric Anesthesia, 20: 240–45, 2010.
41. Bui T, Redden RJ, Murphy S. A comparasion study between Ketamine and Ketamine-promethazine combination for oral sedation in pediatric dental patients. Anaesth Prog, 49(1): 14–18, 2002.
42. Damle SG, Gandhi M, Laheri V. Comparision of oral ketamine and oral midazolam as a sedative agent in pediatric dentistry. J Indian Soc Pedod Prev Dent, 26(3): 97–101, 2008.
43. Alfonzo-Echeverri EC, Berg JH, Wild TW, Glass NC. Oral ketamine foe pediatric outpatient dental surgery sedation. Pediatr Dent, 15: 182-185, 1993.
44. Petros AJ. Oral ketamine its use foe mentally retarded adults requiring day care dental treatment. Anaesthesia, 46: 646–47, 1991.
45. Rosenberg M. Oral ketamine for deep sedation of difficult to manage children who are mentally handicapped: case report. Pediatr Dent, 13: 221–23, 1991.
46. Moore PA, Mickey EA, Hargroves JA, Needleman HI. Sedation in pediatric dentistry: a practical assessment procedure. J Am Dent Assoc, 109: 564–69, 1984.
47. Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: Comparison of two delivery systems with assessment of intra-observer variability. Br J Anaesth, 81: 865–69, 1998.
48. Ljungman G, Krueger A, Andreasson S, et al. Midazolam nasal spray reduces procedural anxiety in children. Pediatrics, 105: 73–78, 2000.
49. Thum P, Heine J, Hollenhorst J, et al. Midazolam given as an intranasal spray in children. Br J Anaesth, 81: 100–01, 1998.
50. Gudmundsdottir H, Sigurjonsdottir J, Masson M, et al. Intranasal administration of midazolam in a cyclodextrin based formulation: Bioavailability and clinical evaluation in humans. Pharmazie, 56: 963–66, 2001.
51. Hannallah R.S. and Patel R.I. Low dose intramuscular ketamine for anesthesia preinduction in young children undergoing brief outpatient procedures. Anesthesiology, 70: 598–600, 1989.
52. Hollister G.R. and Burn JNB. Side effects of ketamine in pediatric anesthesia. Anesth Analg, 53: 264–7, 1974.