A Comparative Evaluation of Intranasal Midazolam, Ketamine and their Combination for Sedation of Young Uncooperative Pediatric Dental Patients: A Triple Blind Randomized Crossover Trial

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***Objective**: The purpose of this study was to evaluate and compare the efficacy and safety of intranasal (IN) administration of midazolam (M), ketamine (K) and their combination (MK) to produce moderate sedation in young, uncooperative pediatric dental patients. **Study design**: In this three stage crossover trial forty five uncooperative ASA type-1 children, who required dental treatment, were randomly assigned to receive one of the three drugs/combination by IN route during three subsequent visits. The efficacy and safety of the agents were assessed by overall success rate and by monitoring of vital signs, respectively. **Results**: The onset of sedation was rapid with K as compared to M and MK. The difference was statistically significant (P< 0.01) between K and M. The overall success rate was 89% with K, MK was 84% and 69% with M. The difference between the overall success rates of K and M was statistically significant (P< 0.01). Vital signs were within physiological limits and there were no significant adverse effects with any medication. **Conclusions**: M, K and MK are safe and effective by IN route to produce moderate sedation for providing dental care to pediatric dental patients who have been otherwise indicated for treatment under general anesthesia.*

***Keywords**: Intranasal route, moderate sedation, analgesia, midazolam and ketamine*
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INTRODUCTION

The delivery of dental care to children can be quite challenging. Majority of children accept dental treatments without any fuss. However, young, fearful and uncooperative children or those with negative behaviors require measures for behavior modification prior to dental procedures.[1] Though conventional behavioral modification techniques can enable us to deliver dental care to few of these children, still many such children may need use of pharmacological methods such as moderate sedation or general anesthesia (GA). Due to high cost, question of parental acceptability and complications associated with GA, it is thought to be the last choice for providing dental treatment.[2,3] Thus, moderate sedation is considered as a more viable option for such children.

For years pediatric dentists all over the world have searched for the ideal sedatives and route of administration to provide moderate sedation. Hence, several types of drugs and various routes have been tried to this end. These routes have their own advantages and disadvantages. The oral route is the most preferred[4] but children may aversive due to bitter taste. Moreover, slow onset of action, prolong recovery and high first pass metabolism are other disadvantages. Although, rectal route is safe, painless and reasonably reliable method in younger children,[5] it may be unacceptable and embarrassing to the older children and dental staff involved.[6] A number of health care providers have also been using more effective intravenous or intramuscular routes owing to rapid onset and early recovery. But these routes are painful and could increase the anxiety associated with treatment.

Hence, in the field of pediatric dental sedation a newer route- IN route has gained momentum due to several significant advantages. The nasal mucosa has a rich vascular supply, so immediate absorption of drugs takes place[7] directly in the systemic circulation avoiding first pass metabolism,

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thus, increasing bioavailability of the drug.[8] Moreover, it is a simple, effective method requiring the least of patient's cooperation during administration[1] and lastly no strict sterile technique is needed.

M, a benzodiazepine with rapid onset and ultra short duration of action has been commonly used by oral route for moderate sedation of pediatric dental patients.[9,10] However, due to its unpleasant taste, addition of some sweetening agent becomes necessary, thereby, increasing the volume of medication. IN administration of midazolam has been shown to have a higher bioavailability and more rapid onset of action.[11-13]

K, a phencyclidine derivative is a sedative, analgesic and premedication agent. It has been reported to be quite safe, effective and useful by oral route.[14-19] However, by oral route its bioavailability is only 16 % due to poor absorption and extensive first pass metabolism, while it is around 93% after parenteral administration.[20]

The combination of M and K has also been used for moderate sedation through enteral.[21] and parenteral[22] routes, including IN route, and has been documented to be safe and effective [23] in medical setting in children. However, the literature has isolated reports regarding the role of MK by IN route to facilitate dental procedures in pediatric dental patients.[24]

Therefore, the present triple blind, randomized clinical trial was envisaged to evaluate and compare the efficacy and safety of IN administration of M, K and MK for moderate sedation of young and uncooperative pediatric dental patients.

METHOD AND MATERIALS

The research protocol of the study was reviewed and approved by the Institutional Ethics Committee, CSM Medical University, Lucknow, India. The possible risk and discomforts, as well as the benefits of the procedure were explained to the parents/guardians and their written consent was obtained before enrolling their wards in the study. Children aged between 2-6 years, having physical status of ASA type I, in whom basic behavior modification techniques were not successful in providing dental treatment and, hence, indicated for treatment under GA (patients having score-1 or 2, Table 1)[25] and whose treatment necessitated administration of local anesthetic injection were recruited in the study. The children who had not taken dental treatment previously were enrolled in the study. The children who had known hypersensitivity to benzodiazepines and K or who were on a medication that was likely to interfere with M or K, were excluded from the study. At the time of enrollment of patients, a comprehensive evaluation in respect of general health including tonsil and adenoid assessment, mouth breathing, speech, hypo-nasality, snoring, airway and chest examination was performed by a Professor of the Department of Anesthesiology, CSM Medical University, Lucknow. The parents/guardians were instructed to bring the children with food restrictions—4 hours for solids and 2 hours for clear liquids on the day of dental treatment.

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

The sample size required to detect a difference of 1.2 min (pooled SD=1.28) in onset of sedation between two groups, with 80% power and 95% confidence limit was estimated to be around 42. Therefore, forty five pediatric outpatients who met the inclusion criteria were enrolled in the study. A triple-blind, randomized, prospective, 3 stage crossover design was adopted in this study. The drugs used were M (0.3mg/kg), K (6mg/kg) and MK (0.2mg/kg and 4mg/kg respectively).

The patients were given all the three drugs/combination on three different visits in a crossover manner. During each sedation/ treatment session the children were evaluated for the time of onset, depth of sedation, behavior / response during dental treatment (ease of treatment completion), changes in vital signs, the oxygen saturation levels, adverse effects, recovery time and the overall success with sedation. However, the main outcome measured was the overall success of treatment session (treatment outcome).

To keep the volume of the drugs minimal for IN administration, concentrated solution of the individual drugs had to be used. M was available in the required concentration while K was not available in concentrated form. So for the purpose of this study it was manufactured by 'Kwality Pharmaceutical Ltd' in the concentration of 100 mg/ml on a special request to the company. To maintain uniformity throughout the study only one brand of each drug was used- Midazolam Hydrochloride (trade name Mezolam 5 mg/ml, Neon Laboratories Ltd) and Ketamine Hydrochloride (Ketamine 100 mg/ml, Kwality Pharmaceuticals Ltd). In order to maintain the triple blind nature of the study the drugs and their combination were coded accordingly by a post graduate resident doctor, under guidance of a Professor of the Department of Pharmacology, CSM Medical University, Lucknow. It was a crossover trial hence all the patients received all three drugs. The order in which they were administered was generated

using an online randomization generator.

On the day of dental treatment, the children were re-evaluated by an anesthesiologist who was present throughout the procedure and also knew the drug/combination being administered so that he was prepared to face any inadvertent reaction of the drugs/combination. The children were weighed and their vital signs i.e., heart rate, respiratory rate, blood pressure and the peripheral oxygen saturation levels were recorded. All the dental procedures were carried out by the author himself, while all other observations and recordings were done by a colleague. The dental treatment procedures for each patient were standardized in such a way that similar procedures were performed in all the three visits. The drugs were administered into both the nostrils in equal volume, with the child in semi recumbent position or in parent's lap using an insulin injection syringe without needle. The child's acceptance of IN drug administration, as well as any possible complication such as burning sensation, coughing, sneezing, etc were carefully assessed and recorded. After the onset of sedation the vital signs and the oxygen saturation were recorded at regular interval of 5 minutes. All patients were given injection of local anesthesia (2% lignocaine with 1:200000 adrenaline) either in the form of nerve block or infiltration. 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 also documented. The treatment sessions was aborted if the patient became highly uncooperative, and dental care could not be performed even with the use of physical restraints. The presence of any side effects or complications was also recorded.

The two parameters, "Ease of treatment completion" and the "Level of sedation", were measured using separate 5 point scales which were used in previous study conducted at our centre[25] (Table 1 and 2). Basically these scales were modified from "AAPD sedation record." The above ratings were recorded at regular interval of 5 minutes. Calibration involved rating of recorded video-graphic 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 also conducted in our department.[9,10] Spearman rank correlation found high inter reliability between the ratings of author and professor ($r = 0.828$, $p<0.001$). Around 20 sedation sessions were randomly chosen and the level of sedation and ease of treatment completion were rated by the professor along with the author during these sessions, in order to assess the reliability of author ratings.

After the completion of the treatment patient was transferred in a quiet room for recovery. 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[26] and an Aldrette score[27] of 9 or greater was achieved. The parent/guardian accompanying the child patient was provided post-procedural instructions along with emergency telephone number and was contacted next day to enquire about any delayed untoward reactions such as vomiting, hallucination, sleep disturbances, etc.

Table 2. 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.

The treatment outcome was considered ' 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 parameters remained within 10% of baselines values, (3) Oxygen saturations levels remained at 90% or greater, (4) Physical restraints were not required during the dental procedure and (5) No major side effects were observed during or after sedation sessions.

Statistical analysis

The effect of drugs (M, K, and MK) on vital signs, oxygen saturation, onset time of sedation and recovery time were compared *interse* by one way analysis of variance (ANOVA) and the significance of mean difference between the drugs groups was done by Newman-Keuls post hoc test. Data were first transformed to square root transformation and then homogeneity of variance among groups was tested by Bartlett's test. All analyses were performed on transformed data. The difference in the depth of sedation, response/behavior during treatment and treatment outcome between the three groups were analyzed by χ^2 test as the response variables for all these parameters had only two possible outcomes (adequate/inadequate; satisfactory/unsatisfactory and successful/unsuccessful. A two-tailed ($\alpha=2$) 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

In this trial all 45 patients (female=22 and male=23) were treated consecutively with three drugs/combination (M, K and MK), thus, making a total of 135 sedation sessions. The age of all patients ranged between 2-6 yrs with mean (± SD) of 4.62 ± 1.43 yrs and mean (± SD) weight of 13.29 ± 3.23 kg. The results obtained have been summarized in Table 3.

Table 3. Primary outcome measures of patients treated with three different drug groups

Parameter		M	K	MK	'p' value
Onset of sedation (min) n=45*	Mean Range	6.80±1.53 (5-10)	5.79±1.42 (5-8)	5.99±1.41 (4-10)	'p'<0.0031 (ANOVA)
Adequate depth of sedation (n%)		38 (84%)	42 (93%)	40 (89%)	'p'<0.4066 (x^2 test)
Ease of treatment completion –'satisfactory' session (n%)		32 (72%)	41 (92%)	38 (84%)	'p'<0.0411 (x^2 test)
Recovery time (min)	Mean Range	31.69±3.37 (26-40)	39.98±3.18 (34-46)	41.21±4.44 (35-49)	'p'<0.001 (ANOVA)
	Number of sessions$	38	42	40	
Treatment outcome – 'successful' session (n%)		31 (69%)	40 (89%)	38 (84%)	'p'<0.0411 (x^2 test)
'Unsuccessful' sessions (n%)	Sessions completed with physical restraints	6 (13%)	3 (7%)	4 (9%)	
	Aborted sessions	8 (18%)	2 (4%)	3 (7%)	

* n = 45, implies the number of sessions; $ recovery time calculated only from those children who were 'adequately' sedated throughout the session.

There was significant differences (F= 6.259, p= 0.0025) in the duration required for the onset of sedation between the three groups, except for the onset of sedation between K and MK which was non-significant (p>0.05). K had fastest onset with a mean duration of 5.79 minutes while M had a slowest onset with a mean duration of 6.80 minutes. Similarly there were significant differences in the duration required for the recovery (F=74.060, p<0.0001). The mean recovery time in children sedated with both K and MK was found to be significantly (p<0.001) longer as compared to children sedated with M. In the same way, the mean recovery time in children sedated with MK was also found to be significantly longer (p<0.05) as compared to subjects treated with K. Thus, children recovered fastest when sedated with M (31.69) and slowest when sedated with MK (41.21). K provided 'adequate' depth of sedation during maximum number of sedation sessions (93%) and provided 'satisfactory' completion of treatment during 41sedation session, while ease in completing treatment was least with M.

ANOVA 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 10% 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, taking place three times with K and once with MK. However, it occurred after the completion of treatment session, thus, did not affect the delivery of the treatment.

The overall success rate (treatment outcome), was most successful with K (89%) while least successful with M (69%). The combination (MK) was having overall success rate of 84% i.e., between K and M. Thus, in the present study, the overall success rate of these three regimens was significantly higher with K. The combination of M and K was better than M alone but does not provide any advantage over K alone.

DISCUSSION

A number of studies have been carried out with these and other drugs using oral route[9,10,18,19] but there are only isolated reports of use of M, K, and MK by IN route to produce moderate sedation in pediatric dental patients.[28-30] This route has been used primarily as a mean of circumventing the need for injection or bitter tasting oral drugs in children[31] especially in unwilling patients.[32,33] Being, 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, infection associated with intramuscular injection, etc. Moreover, it has also been shown that IN M, K and their combination when used as premedication are devoid of respiratory and cardiovascular depression[34] Absorption of IN drugs occurs directly into the systemic circulation, avoiding first pass metabolism[35] and resulting in rapid onset of action. It has also been reported that this faster onset may also be due to the rapid achievement of adequate cerebrospinal fluids level of the drugs due to the communication to the subarachnoid space via the olfactory nerve and its sheath.[36-38]

Coughing and sneezing with IN administration of the drugs has been reported by various workers[29,39,40] and has been attributed to the probable large volume of medication.[4] In the present study careful administration of small volume of drugs and proper posture, sneezing was observed only in very few cases. (4 out of 135 sessions 2.94%). One study has reported that the patients complained of burning sensation on IN administration of M[42] but even this did not occur in our study.

The only complaint was bitter taste by some patients when some of the drug solution moved from nasal cavity downwards into oro-pharynx. However, subsequent analysis led us to believe that even it could be avoided by using lesser volume with higher concentration of drugs so that the drug solution is restricted to naso-pharynx only. Emergence reactions is a well established adverse effects of K, however, it did not develop in any of our patients. Some other workers have either reported absence of emergence phenomenon in children with low dose of K[43,17] or lower incidence (5%) as compared to adults (>30%).[44]

Although nausea and vomiting are also known side effects of K it was observed only on three occasions with IN-K and only once with IN-MK in our study. 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 aspect in respect of moderate sedation are crucial- onset, depth and duration of sedation. An ideal agent and route would be which has quick onset of action and provides sufficient depth of sedation. The duration is also very crucial. It should be neither too short for the dental procedure nor too prolonged thus necessitating unnecessary stay of the child in the dental clinic. In our study we employed IN route to obtain quick onset of action without giving pain as with intravenous or intramuscular route. Moreover, all the drugs/combination gave us the adequate depth of sedation and sufficient time to complete dental treatment requiring relatively less recovery time. These properties of IN route providing quick onset, adequate depth of sedation, and short period of recovery observed in our study are in concurrence with other studies also.[1,13,31]

CONCLUSION

Intranasal route is safe and effective mode of drug administration in moderate sedation. Intranasal administration of midazolam, ketamine and their combination all proved to be easy to administer, had a rapid onset of sedation and considered safe and effective for moderate sedation. However, intranasal ketamine was found to have the highest overall success rate in modification of behavior of the uncooperative pediatric dental patient to accept treatment. The combination of midazolam and ketamine provides no benefits as compared to ketamine but is better than midazolam alone.

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