

A Comparative evaluation of Intranasal Dexmedetomidine, Midazolam and Ketamine for their sedative and analgesic properties: A Triple Blind Randomized Study

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Objectives: To evaluate and compare the efficacy and safety of Intranasal (IN) Dexmedetomidine, Midazolam and Ketamine in producing moderate sedation among uncooperative pediatric dental patients. **Study Design:** This randomized triple blind comparative study comprises of eighty four ASA grade I children of both sexes aged 4-14 years, who were uncooperative and could not be managed by conventional behavior management techniques. All the children were randomized to receive one of the four drug groups Dexmedetomidine 1µg/kg (D1), 1.5µg/kg (D2), Midazolam 0.2mg/kg (M1) and Ketamine 5mg/kg (K1) through IN route. These drug groups were assessed for efficacy and safety by gauging overall success rate and by monitoring vital signs, respectively. **Results:** The onset of sedation was significantly rapid with M1 and K1 as compared to D1 and D2 ($p < 0.001$). The overall success rate was highest in D2 (85.7%) followed by D1 (81%), K1 (66.7%) and M1 (61.9%), however, the difference among them was not statistically significant ($p > 0.05$). Even though all the vital signs were within physiological limits, there was significant reduction in pulse rate (PR) ($p < 0.001$) and systolic blood pressure (SBP) ($p < 0.05$) among D1 and D2 as compared to M1 and K1. D1, D2 and K1 produced greater intra- and post-operative analgesia as compared to M1. There were no significant adverse effects with any group. **Conclusion:** Dexmedetomidine, Midazolam and Ketamine, all the three drugs evaluated in the present study can be used safely and effectively through IN route in uncooperative pediatric dental patients for producing moderate sedation.

Keywords: Intranasal, Dexmedetomidine, Midazolam, Ketamine, sedation, children.

INTRODUCTION

Pain, fear, anxiety and anger are the main emotional components to be dealt by a pedodontist while treating a child. Pedodontics, as a specialty, recognizes that behavioral management of child cannot be separated from the quality of the dentist's work.¹ Although, most of the uncooperative pediatric dental patients can be managed through conventional behavior management techniques but, some are unable to tolerate dental treatment comfortably despite these. In such cases pharmacological means

of management of patients are helpful. It mainly includes various modalities of moderate sedation and general anesthesia (GA). GA is considered as last choice due to its high cost and the complications associated with it as it interferes with the physiology of the patients. Moderate sedation has been found to be more effective in carrying out the most comfortable, efficient and high quality dental services to the patient and also to develop a positive attitude towards future dental treatment.

Various pharmacological agents have been used through different routes for moderate sedation in pediatric dentistry. Every route of administration has own advantages and disadvantages. Among various routes, intranasal (IN) route is highly preferred route for sedating pediatric dental patients, as it is non invasive, helps in rapid absorption of the drug, enables quick post-operative recovery and leads to high bioavailability of drug. This route is highly acceptable by pediatric patients, also.² But, this route is very rarely used by pediatric dental care providers.

Dexmedetomidine (D) is a comparatively newer drug, an α_2 agonist, a novel sedative with analgesic properties that controls stress, anxiety and pain. It produces stable respiratory rate and predictable cardiovascular responses and currently it is widely used in pediatric patients. Besides other routes, D is conveniently and effectively given by IN route also and it is well tolerated.^{4,45}

Midazolam (M), an ultra short acting sedative, amnesiac and anxiolytic, is widely used in children by virtue of its greater margin of its safety. Midazolam is 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.³

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Table 1. Sedation Rating Scale

Score	Classification	Behavioral sign
1	No sedation	Typical response/ cooperation for this patient
2	Minimal	Anxiolysis
3	Moderate	Purposeful response to verbal commands ± light tactile sensation
4	Deep	Purposeful response after repeated verbal or painful stimulation
5	General anesthesia	Not arousable

Ketamine (K) is a phenylcyclidine derivative used widely in pediatric patients because of its hypnotic, analgesic and amnesic effect. ketamine is safe and effective by either mode of IN drug administration for moderate sedation in facilitating dental care for anxious and uncooperative pediatric dental patients.⁴

The objectives of the present study were to evaluate and compare the efficacy of IN D, M and K in producing moderate sedation among pediatric dental patients.

MATERIALS AND METHOD

Children of both sexes aged between 4 to 14 years, who were fearful/anxious and for whom basic behavior guidance techniques had not been successful in rendering dental treatment (score 1 or 2 in Table 2)⁶ and hence indicated for treatment under GA, were recruited for the study. All the children were healthy, ASA grade I and without any history of previous dental treatment under sedation or anesthesia and whose treatment necessitated the administration of local anesthesia. Only the patients whose parent/guardian willfully gave written consent, after being explained about risk and possible discomfort involved in the study, were included in the study. Exclusion criteria included known allergy or hypersensitive reactions to any of the test drugs.

A brief medical history was enquired from the parent or the guardian. All the patients proposed to be selected for the study, were examined by an anesthetist from Department of Anesthesiology to assess their general health and airway suitability for undergoing sedation. Airway assessment included evaluation of neck mobility, Size of jaws, tongue / tonsils, obstruction in the airway (adenoids), extent of mouth opening and obesity (interference in ventilation). The guardian was also instructed to keep the child on NPO (*nil per os*) -4 hours for solid diet and 2 hours for clear liquids, on the day of treatment.

The present study was randomized and kept triple blind in order to eliminate all kinds of bias. Eighty four (43 male and 41 female) pediatric patients ranged from 4-14 years of age and weight ranged from 9 to 27 kgs. The drugs used in four groups were, D1 (Dexmedetomidine- 1 µg/kg) and D2 (Dexmedetomidine- 1.5µg/kg), M1 (Midazolam-0.2mg/kg) and K1 (Ketamine- 5mg / kg)

To deliver drugs by IN route, the quantity of drugs should be kept minimum; as large volume of drug is difficult to deliver through the nose hence concentrated solution of the individual drug was used. In order to maintain uniformity throughout the study only one brand of each drug was used- Dexmedetomidine hydrochloride (Dexmedit 100µg/ml, Neon laboratories), Midazolam Hydrochloride (Mezolam 5 mg/ml, Neon laboratories) and Ketamine Hydrochloride (Aneket 50mg/ml, Neon laboratories). The drugs were coded accordingly by a Professor of the Department of Pharmacology, King George’s Medical University, Lucknow, to maintain the triple blind nature of the study. The order of the drugs was randomized using an online randomization generator.

According to randomization all the drug solutions were prepared by a senior resident of the Department of Pedodontics (who was not a part of the study), on the day of sedation session. Depending upon the dosages calculated from the weight of the children, all the drug solutions were prepared from parenteral solutions and made to an equal final volume of 2 ml by adding normal saline.

On the day of treatment, the clinical status of the child was re-evaluated by an anaesthesiologist who was present throughout the procedure and also knew the drug being administered so that he was prepared to face any inadvertent reaction of the drugs. The vital signs and oxygen saturation levels were re-examined and recorded in the sedation chart. The drugs were instilled into both nostrils using a 1-mL syringe (without needle) with the child in the recumbent position. 0.2ml of drug solution was instilled slowly in each nostril alternately with an interval of 30 seconds between each administration until the complete drug dose was instilled. The time of drug administration was recorded. When the sedative effect began to appear, the time of onset was again recorded. After the onset of sedation, pulse rate, blood pressure, oxygen saturation and respiratory rate were recorded regularly at 5 minutes interval. Local anaesthesia (LA) was administered in the form of nerve block (2% Lignocaine with 1:200000 Adrenaline) in all the patients. Same procedure (extraction) was performed in all the patients. All the dental procedures were carried out by the author himself while observations and recordings were done by a colleague. Use of physical restraints during the procedure was also documented. The

Table 2. Behavior / Response to Treatment (Ease of Treatment Completion) Rating Scale

Score	Classification	Behavioral sign
5	Excellent	Quiet and cooperative
4	Good	Mild objections &/or whimpering but treatment not interrupted
3	Fair	Crying with minimal disruption to treatment
2	Poor	Struggling that interfered with operative procedures
1	Prohibitive	Active resistance and crying; treatment cannot be rendered

treatment session was aborted if the patient became highly uncooperative even with the use of physical restraints. The patients were observed for adverse effects both during the procedure and as well as during the recovery periods.

The children were evaluated for the time of onset, depth of sedation, behaviour/response during dental treatment (ease of treatment completion), changes in vital signs, oxygen saturation levels, adverse effects, recovery time and the overall success with sedation. However, the main outcome measured was, the overall success of the treatment session.

The “level of sedation” and “Ease of treatment completion” were measured using separate 5 point scales (Table 1 and 2) which have been modified from “AAPD sedation record”. These scales have also been used in previous studies conducted at our centre.^{2,6} In order to assess the reliability of author ratings, around 20 recorded video-graphic segments of the sedation sessions were randomly chosen and the ‘level of sedation’ and ‘ease of treatment completion’ were rated by a professor in the department of pediatric dentistry who was involved in previous studies conducted in our department.^{7,8}

- 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.
- 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.

Intra- and post-operative analgesic effect was measured using the Face, Legs, Activity, Cry and Consolability (FLACC) scale. The FLACC pain scale was chosen because it has been designed for children between the ages of 2 and 7 and for people who are unable to properly communicate their pain properly during sedation.¹⁰

The sedation session was considered safe and successful if -

1. Physiological parameters remained within clinically acceptable ranges (within 10% of baseline values).
2. Oxygen saturation remained at 90% or greater;
3. Level of sedation was satisfactory (score of 2or 3 throughout the treatment).

4. Overall behavior during treatment (ease of treatment completion) was satisfactory (score of 4 or 5 throughout the treatment).
5. Use of restraint for dental treatment not required.
6. Absence of any adverse effect during and after analgo-sedation sessions.

Once the treatment was completed, patient was transferred to a quiet room free from disturbances for recovery. Once fully recovered the vitals were rechecked and the patient was discharged when the AAPD sedation guidelines criteria for discharge were met¹¹ and an Aldrette score¹² of 9 or greater was achieved. The care taker was clearly explained about the post-operative instructions along with emergency telephone number and also requested to complete a questionnaire about adverse effects in the next 24 hours. All the results obtained in this manner were recorded on a sedation record chart. The results were put through various statistical tests and the decoding was done only when the analysis was completed.

Statistical Analysis

Statistical analysis of the available data was carried out to ascertain the statistical level of significance of various observations. Continuous data were summarized in Mean ± SD while discrete (categorical) in %. The effect of four drug groups (D1, D2, M and K) on six different parameters (oxygen saturation, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, onset of sedation) were compared together by one way analysis of variance (ANOVA) and the significance of mean difference between the groups (drugs) was done by Tukey’s HSD (honestly significance difference) post hoc test. Categorical data (depth of sedation, ease of treatment and overall success rate) was analyzed by χ^2 test as the response variables for all these parameters had only two possible outcomes. 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 *Statistica* (window version 6.0).

RESULTS

The age of Groups M, K, D1 and D2 were 4-12 yrs, 4-11 yrs, 4-11 yrs and 4-11 yrs, respectively with mean (\pm SD) 7.34 ± 2.34 yrs, 6.71 ± 2.31 yrs, 7.76 ± 2.26 yrs and 7.24 ± 2.36 yrs, respectively. Comparing the mean age of four groups, ANOVA revealed similar age among the groups ($F=0.75$, $p=0.525$). Comparing the

Table 3. Primary Outcome Of Patients (Mean ± SD, n=21) in Different Groups

Characteristics	D1	D2	M	K	p value
O2 saturation (%)	99.01±0.59	98.96±0.30	98.99±0.35	99.02±0.43	0.972
Respiratory rate (breathe/min)	21.00±0.62	20.91±0.70	21.09±0.62	20.65±0.77	0.193
DBP (mmHg)	70.40±5.90	70.24±5.11	72.08±3.95	73.15±4.04	0.159
Pulse rate (beats/min)	101.31±6.86	101.42±2.93	112.92±7.41	114.48±5.89	p<0.001
SBP (mmHg)	99.21±8.55	99.41±8.59	104.84±4.07	105.91±3.95	0.001
Onset time (min)	18.24±2.00	18.10±2.00	10.43±1.83	11.57±2.18	p<0.001
Recovery time (min)	59.81±5.89	62.24±7.17	40.71±2.45	44.19±5.24	p<0.001
Intra operative analgesia (score)	3.81 ± 0.81	3.67 ± 0.91	5.62 ± 1.12	3.52 ± 0.68	p<0.001
Post operative analgesia (score)	1.29 ± 0.90	1.14 ± 0.65	2.81 ± 0.60	1.10 ± 0.89	p<0.001

Table 4. Frequency Distribution Of Overall Success Rate In Different Groups

Overall success rate	D1	D2	M	K	χ^2 value (DF=3)	p value
Satisfactory	17 (81.0%)	18 (85.7%)	13 (61.9%)	14 (66.7%)	4.19	0.242
Unsatisfactory	4 (19.0%)	3 (14.3%)	8 (38.1%)	7 (33.3%)		

Table 5. Frequency Distribution of Overall Sedation Level in Different Groups

Overall sedation level	D1	D2	M	K	χ^2 value (DF=3)	p value
Satisfactory	19 (90.5%)	20 (95.2%)	15 (71.4%)	16 (76.2%)	5.83	0.120
Unsatisfactory	2 (9.5%)	1 (4.8%)	6 (28.6%)	5 (23.8%)		

proportions (F/M) of genders between the groups, χ^2 test revealed similar proportion of genders among the groups ($\chi^2=1.29, p=0.732$). Similarly, the weight of Groups M, K, D1 and D2 ranged from 14-15 kg, 11-23 kg, 11-24 kg and 10-26 kg, respectively with mean (\pm SD) 18.29 \pm 3.04 kg, 16.52 \pm 3.87 kg, 18.57 \pm 4.17 kg and 17.71 \pm 5.36 kg, respectively. Comparing the mean weight of four groups, ANOVA revealed similar weight among the groups ($F=0.98, p=0.405$).

All the drugs were well accepted by all the subjects through IN route. The mean \pm SD value of oxygen saturation, respiratory rate (RR) and diastolic blood pressure (DBP) during sedation with M, K, D1 and D2 were summarized in table 3. The analysis of variance (ANOVA) revealed that the effect of four drugs on these three parameters was statistically insignificant. Further, pair wise comparison of means also showed that the oxygen saturation level in four drug groups did not differ significantly ($P>0.05$).

The mean \pm SD value of PR and SBP during analog-sedation with D1, D2, M1 and K1 were summarized in table 3. ANOVA revealed that the effect of four drugs on PR and SBP was statistically different. Further, the Tukey test revealed significantly lower PR and SBP in both D1 and D2 groups as compared to both M1 and K1 groups. However, the difference in PR and SBP among the groups D1 and D2 was statistically insignificant ($p>0.05$). Similarly the difference among the groups M and K was also statistically insignificant ($p>0.05$). (Table 3)

ANOVA revealed that the onset time and recovery time of four drugs was statistically different. Further, the Tukey test revealed significantly different and grater onset and recovery times of both D1 and D2 as compared to both M1 and K1. However, the difference in onset and recovery time among the groups D1 and D2 was statistically insignificant. Similarly the difference among the groups M and K was also statistically insignificant ($p>0.05$). (Table 3)

ANOVA also revealed that intra- and post-operative analgesic effect of the four drugs were statistically different. Further, the Tukey test revealed significantly lower intra- and post-operative analgesia score in D1, D2 and K1 as compared to M1. However, the difference in intra- and post-operative analgesia score among the groups D1, D2 and K1 was statistically insignificant ($p>0.05$). (Table 3)

The distribution of overall success rate of four groups is summarized in Table 4. In all four groups, the success rate was highest in D2 (85.7%) and M1 the least (61.9%). Comparing the proportions (S/U) of overall success rate of four groups, χ^2 test revealed similar proportion of success rate among the groups ($\chi^2=4.19, p=0.242$) i.e. not differed statistically.

The distribution of overall sedation level of four groups is summarized in Table 5. In all four groups, the sedation was highest in D2 (95.2%) and least in M1 (71.4%). Comparing the proportions (S/U) of overall sedations of four groups, χ^2 test revealed similar proportion of sedation among the groups ($\chi^2=5.83, p=0.120$) i.e. not differed statistically. However, there was observed clinical difference.

In all four groups, the satisfactory behaviour was highest in D2 (90.5%) and least in M1 (71.4%). Comparing the proportions (S/U) of overall behaviour of four groups, χ^2 test revealed similar proportion of overall behavior among the groups ($\chi^2=3.09, p=0.378$) i.e. not differed statistically. (TABLE 6)

DISCUSSION

In the present study two drugs, Midazolam (M), Ketamine (K) were used in single dose as mentioned earlier while the third drug Dexmedetomidine (D), was used in two doses 1 μ g/kg (D1) and 1.5 μ g/kg (D2). Since long time M, K and their combination have been used as sedative and pre-medicative agents.^{26,28} In pediatric dentistry M and K are well recognized medication for moderate sedation. But D is comparatively newer drug, widely used as a sedative and pre-medicative agent in present era. Various researchers have used these drugs through different routes and found their safety and efficacy through each route.^{22,39,40}

Time of Onset

The present study shows that D1, D2, K1 and M1 all provide good analgo-sedation when administered by IN route. The time required for the onset of sedation is an important property used to evaluate the efficacy of any sedative. As stated by various authors,¹³⁻¹⁵ in the present study also the onset of sedation was most rapid with M1 followed by K1, D1 and D2. It can be a very important clinical finding because it shows that M1 and K1 attain the desired effect by

Table 6. Frequency Distribution of Overall Behaviour in Different Groups

Overall Behavior	D1	D2	M	K	χ^2 value (DF=3)	p value
Satisfactory	18 (85.7%)	19 (90.5%)	15 (71.4%)	16 (76.2%)	3.09	0.378
Unsatisfactory	3 (14.3%)	2 (9.5%)	6 (28.6%)	5 (23.8%)		

IN route as compared to D1 and D2 given by same route. The onset time of K1 in this study is delayed than previous work³ (4-8 mins), in which the dosage was different (6mg/kg). But, for both the doses of D (D1 and D2), it is similar as compared to the results of other works.^{15,16} There is paucity of literature regarding the comparative evaluation in respect of onset of sedation by these drugs when these drugs were given by IN route.

The relative changes in the vital signs observed during treatment were not significant on intergroup comparison except pulse rate (PR) and systolic blood pressure (SBP). PR and SBP were found to be significantly reduced among D1 and D2 as compared to M1 and K1, but these did not need any clinical intervention. Many other workers have also reported similar decrease in blood pressure and PR with D administration.^{20,21} Despite of this clinical effect D produced a safe and effective sedation like other studies.²²⁻²³ Regarding M1 and K1 all the vital signs remained stable during all the sedation sessions like earlier studies.²⁴⁻²⁶

Recovery Time

On comparing the recovery times of these drugs we found that recovery was fastest with M1 and it was in accordance with previous result that suggest faster recovery after M administration when used orally¹⁷⁻¹⁹ and intranasally.¹² The recovery time of K1 was found to be slightly longer than M1. The above outcome in respect of recovery times in our study was similar to the results of earlier study.³ D1 and D2 were observed with longest recovery when compared to M1 and K1. The differences were found to be statistically significant. The recovery times of D1 and D2 are similar to the previous results.¹⁵

Analgesic Effect

Various authors have shown that IN K produces significant analgesia both during intra- and post-operative period.²⁷⁻²⁹ The above observations are in accordance with results of present study as K1 is good among the four groups, both intra- and post-operative, followed by D2, D1 and M1. M1 produced a significantly lower analgesia when compared to other groups. This finding is well understood, because M does not possess analgesic activity but the analgesic effect observed may be due to generalised depression of the CNS. The fear of needle while administering local anaesthesia was considerably reduced. D1 and D2 also produced analgesia both intra- and post-operatively similar to K1. D produced a very good intra and postoperative analgesia in healthy volunteers when given IV.³⁰⁻³² Also D enhances the effect of lignocaine by enhancing central neural blockades.³³ Lignocaine is the most common LA used during dental procedures. In the present study also lignocaine was used as a LA. Earlier study also stated that IN- D sedation for dental procedures produced excellent intra and postoperative analgesia.²³ So, for dental procedures IN- D can also be used as an analgo-sedative.

Several workers have employed various doses of IN-D, ranging between 0.5µg/kg and 2µg/kg and found that sedation level increases with increase in dosage.^{5,22,45} However, in the above studies IN-D has been used as a premedication. In another study conducted for dental procedures under LA, 1 µg/kg IN-D was used to produce an effective analgo-sedation²³. In the present study two doses (1 and 1.5µg/kg) of IN-D were given to equal number of patients and it was observed that there was no significant difference among the two doses in respect of any parameters of analgo-sedation evaluated. Thus for dental procedures under LA even lower dose of IN-D (1

µg/kg) can be used for producing effective analgo-sedation. Moreover, there was no significant difference in adverse effects also.

Coughing, sneezing and burning sensation in nose has been reported previously with IN administration of the drugs³⁴⁻³⁷ and has been attributed probably to the larger volume of the drug applied.³⁸ Smaller volume and careful method of administering IN drugs in present study might have helped to reduce them to a minimum.

The main complaints were restricted to the bitter taste by some patients when some of the solution moved downwards through nasopharynx but it did not alter the delivery of the drugs. In the present study 2ml drug solution was used hence some of the fluid might have trickled backwards giving rise to bitter taste. However, subsequent analysis led us to believe that even this bitter taste may be avoided by using lesser volume of liquid with higher concentration of drugs. Emergence reactions are well established adverse effects of K; however, these were not detected in our study as in many other studies.³⁹⁻⁴⁰ Moreover, the incidence of emergence reactions in children is reported to be lower (0 to 5%) than in adults (> 30%) patients.⁴¹

In the present study vomiting was the only adverse effect observed in K1 and D1. Although nausea and vomiting are known side effects of K, it was observed only once with K1 and once with D1. However, in both the cases vomiting did not take place during treatment session. It occurred after the completion of treatment session and did not adversely affect the delivery of the treatment during the sedation session. Moreover, when a detail enquiry was made from those parents/guardians of the child patients regarding the following of pre-sedation instructions, it was revealed that the child who received D1 had taken food before the sedation session. Thus, the vomiting in this patient might be associated with the food consumed by the child before coming for the dental treatment. Although in one study it has been reported that IN-M does not increase the incidence of vomiting if food is consumed.¹²

Comparison Between D, M and K

Many of the workers have compared the efficacy and safety of two drugs administered – either M and K³ or M and D⁴⁶, but there is paucity of literature regarding comparison of K and D. Moreover, there is no study reported in which all the three drugs have been compared which has been successfully done in our study. The present study is one further step in search of an ideal agent and its route of administration to induce moderate sedation to child patients. The results of the present study regarding M and K are in agreement with the previous studies.^{3,42} It was observed that K provided better sedation and anxiolysis as compared to M when used for premedication. Further, it has also been observed in other studies that IN-K was better than IN-M and their combination.²⁵ Although there are some reports that M might be more effective than K when oral route is employed.⁴³ However, when agents have been administered by IN route then superiority of K seems to be unquestioned. It may be probably attributed to rapid and almost complete absorption from nasal mucosa. It is also worthwhile to mention that K as a single drug provides both sedation and analgesia while M has only sedative properties.

In our study there is no significant difference between D1 and D2 in all the analgo sedative properties assessed. Many investigators have compared IN- D with oral M and found IN- D to be a better sedative than oral midazolam.^{44-46,22} But there is lack of literature

regarding comparison of IN-D with IN-K and IN-M. The results of the present study showed that IN-D produced safe and effective sedation, comparable to IN- M and IN- K.

CONCLUSION

Intranasal route is safe and effective mode of drug administration for moderate sedation. D1, D2, M1 and K1 have been found to produce good sedation when administered intranasally. IN D produced maximum reduction in SBP and PR among the three drugs evaluated. The difference was found to be statistically significant but clinically it did not need any intervention. The relative changes in the remaining vital signs observed were not significant. D1 and D2 produced significantly greater analgesic property than M1 and as equally as K1. The mean time of onset of sedation and recovery was most rapid for M1 and slowest for D2. Overall, highest success rate was for D2 and least for M1.

Hence, the present study showed that the IN administration of D, M and K all proved to be easy to administer, had a rapid onset of sedation and considered safe and effective for moderate sedation .IN- D produced safe and effective sedation, comparable to IN-M and IN-K. Further studies of larger scale are suggested and also the effects of atomization device in IN-D delivery are to be explored.

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