Intranasal Dexmedetomidine Versus Intranasal ketamine as A Pre-Anesthetic Medication in Pediatrics

Original Article

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ABSTRACT

Introduction: The immediate pre-operative period is stressful, especially for children, and managing pre-operative anxiety is an important concern for anesthetists. Many anesthetic pre-medications are used to alleviate stress. Of these pre-medications, ketamine and dexmedetomidine have been effectively used.

Objectives: To compare intranasal dexmedetomidine versus intranasal ketamine as a premedication in children undergoing surgery regarding sedative effect, successful child–parental separation and effect on hemodynamic parameters.

Study design: After obtaining ethical committee approval and informed parents' consents, this prospective randomized comparative clinical trial was performed in Ain Shams University Hospitals on 90 children aged 1-8 years of either sex, scheduled for minor elective surgeries. Subjects were randomly divided into 2 groups of 45 each. 30 minutes before induction, group D received intranasal Dexmedetomidine (1 mcg/kg), while group K received intranasal Ketamine (2 mg/kg).

Results: The MOAA/S (Modified Observers Assessment of Alertness/ Sedation Scale) scores were significantly lower in group D compared to group K at 10, 20 and 30 minutes after the drug administration. Parent separation score was statistically significant in favor of group D at 10 and 20 minutes of drug administration but with no statistically significant difference between both drugs at 30 minutes. Greater number of children in group D achieved satisfactory sedation of 91.1% which was statistically significant. There was a statistically significant decrease in heart rate and blood pressure in group D 30 minutes after drug administration and during the intraoperative period while no significant difference was observed at 10 and 20 minutes. Also, there was no significant difference in oxygen saturation between the 2 groups. Regarding adverse effects of the drugs, the incidence of shivering was significantly higher in group K than in group D while post operative nausea and vomiting showed no statistically significant difference between both groups.

Conclusion: Intranasal dexmedetomidine and intranasal ketamine can be used effectively and safely as preanesthetic medications in children undergoing surgery under general anesthesia. Both drugs produce effective and favorable sedation levels and acceptable parental separation with superiority of dexmedetomidine in sedation scores. Dexmedetomidine also produces some decrease in heart rate and blood pressure which is favorable during surgery.

Key Words: Intranasal dexmedetomidine, intranasal ketamine, pediatrics, pre-anesthetic medication, sedation.

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INTRODUCTION

The immediate pre-operative period is very stressful, especially for children, and managing pre-operative anxiety is an important concern for anesthetists. Many anesthetic pre-medications are used to alleviate stress. Of these pre-medications, ketamine and dexmedetomidine have been effectively used[1].

Sedative premedications play an important role in pediatric anesthesia, helping patients overcome fear and anxiety and facilitating parental separation. There are many routes for administering sedatives that do not require insertion of a venous line, such as oral, intranasal, intramuscular, and rectal. The intranasal approach is safe, painless, well tolerated, and with a comparable onset of action to the intravenous approach[2]. It also has high bioavailability as it bypasses first-pass hepatic metabolism and because of nasal mucosa rich blood supply[3].

Dexmedetomidine, an α2-adrenoceptor agonist, has excellent sedative and analgesic properties with no respiratory depression. It also attenuates hemodynamic stress response by its sympatholytic action[4].Ketamine as a sedative is commonly used in children. It is an N-methyl D-aspartate (NMDA) receptor antagonist that produces dissociative anesthesia and is known to reduce central sensitization to pain, decrease overall opioid use,

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and produce effective sedation level. It has been used in various ways, most recently intranasal in children[5,2].

The aim of this work was to compare intranasal dexmedetomidine versus intranasal ketamine as a premedication in children undergoing surgery regarding sedative effect, successful child–parental separation and effect on hemodynamic parameters.

PATIENTS AND METHODS

After obtaining ethical committee approval from the Research Ethical Committee, Faculty of Medicine Ain Shams University FMASU MS 230/2023 and informed parents' consents, this prospective randomized clinical trial was performed in Ain Shams University Hospitals on 90 children scheduled for elective surgeries. The subjects were randomly divided into 2 groups; Group D (n= 45) and group K (n= 45).

Inclusion Criteria

Age group: 1-8 years old, ASA I or II, within normal weight range (between 5th to 95th percentile) according to WHO growth chart, and undergoing minor elective surgery.

Exclusion Criteria

Lack of guardians' consent, any known case of allergy to the study drugs, nasal deformity or pathology, recent upper respiratory tract infection (within 2 weeks).

Sampling Method

Patients fulfilling inclusion criteria were randomly divided into two groups using their computer-generated random numbers.

Sample Size

Based on the results of Gupta *et al.*[6], with 53% of patients in ketamine group reaching satisfactory sedation compared to 80% in dexmedetomidine group, alpha error 5% and power of study 80%, the calculated sample size was 90 patients, 45 in each group. The program used for sample size calculation was STATA 10.

Study Procedure

Every patient was subjected to a careful preanesthetic assessment that included clinical history, examination and routine laboratory investigations as complete blood count (CBC). All patients were fasted overnight, and clear fluids were allowed up to 4 hours prior to induction. Children were taken into the preoperative room with one parent allowed to accompany them.

Group D received intranasal dexmedetomidine (1 mcg/ kg) 30 mins before induction.

Group K received intranasal ketamine (2 mg/ kg) 30 mins before induction.

The intranasal dexmedetomidine (100 mcg⁄ ml preparation) and ketamine (50 mg⁄ ml preparation) were prepared according to the patient's body weight so as to dilute the calculated dose of the drug in a total volume of 2 ml. Equal volumes of the drug were dripped into both nostrils using a 3 ml syringe with the child in a recumbent position. The premedication was given in the preoperative holding area in the presence of one parent.

The investigator (anesthesiologist) involved in preparing and administering the drug was different from the one (anesthesiologist) responsible for further assessment and management of the patient. Vital signs (heart rate, blood pressure, oxygen saturation), as well as the degree of sedation and anxiety were recorded before administering the drug and again at intervals of 10 mins, for 30 mins after drug administration.

Measured Outcomes

The primary outcome was assessment of sedation status at 10, 20, and 30 mins after drug administration. The secondary outcomes were successful parental separation, hemodynamic changes and side effects as shivering and postoperative nausea and vomiting.

The degree of sedation was assessed using Modified Observers Assessment of Alertness/ Sedation Scale (MOAA/S) (Appendix 1). The onset of sedation was defined as the time when reaching a MOAA/S score of 5. At the time of induction, a MOAA/S score between 1 and 4 represented satisfactory sedation while 5 or 6 represented unsatisfactory sedation.

The response to parental separation was assessed at the time of transferal to the operation theatre using the Child Parent Separation Scale (Appendix 2). Parental separation at the time of induction was considered successful when the patients were calm, sedated, not crying or agitated allowing smooth induction (score 1).

Children were transported to the operating room where induction with general anesthesia was performed after attachment of routine baseline monitors and insertion of a venous cannula, child's sedation, and successful parental separation were noted. In all children, preoxygenation with face mask using 100% oxygen was performed for 3 mins and induction with IV propofol 2 mg/ kg, fentanyl 2 mcg/ kg, +/- atracurium 0.5 mg/ kg. The child was then intubated with proper size-cuffed endotracheal tube, and after confirmation of capnography, auscultation was done to check for bilateral equal air entry.

Maintenance of anesthesia was done by isoflurane. To avoid hypothermia, a thermal mattress was used during surgery, the temperature of the operating room and PACU (post anesthesia care unit) was kept at 22-26 degrees through out the study .

Vital signs: (Heart rate (HR), mean blood pressure (MBP), oxygen saturation (SpO2)) was recorded every 10 mins for 30 mins after induction of anesthesia.

Incidence of post operative adverse effects such as bradycardia (decrease in HR > 30% of patient's baseline HR or requiring intervention), hypotension (decreased systolic or mean arterial blood pressure > 30% from patient's baseline blood pressure or requiring intervention),nasal irritation, running nose, shivering, disorientation, confusion, or loss of motor coordination, dizziness, PONV (postoperative nausea and vomiting) were observed, recorded after recovery from anesthesia till time of discharge from the PACU and managed accordingly.

Statistical Analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean ± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test.

The following tests were done

- Independent-samples t-test of significance was used when comparing between two means
- Mann Whitney U test: for two-group comparisons in non-parametric data.
- The Comparison between groups with qualitative data was done by using Chi-square test.

P-value <0.05 was considered statistically significant.

RESULTS

Hemodynamic data

Preoperative vital data i.e., heart rate, mean blood pressure and oxygen saturation were statistically similar in both groups. Similarly, after 10 and 20 mins of intranasal drug administration no statistically significant difference was observed in vital parameters between both groups. However, after 30 mins and 40 mins of premedication, heart rate and mean blood pressure were significantly less among children in group D as compared to those in group K. Also, intraoperative heart rate and mean blood pressure were significantly less in those of group D. There was no significant difference in oxygen saturation between the 2 groups. (Figures 1,2)

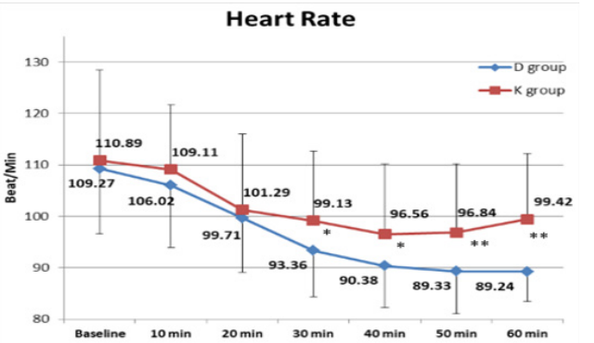

Fig. 1: Comparison between D group and K group regarding heart rate Data are presented as mean ± SD and range. Lines represent mean values and error bars are SD.

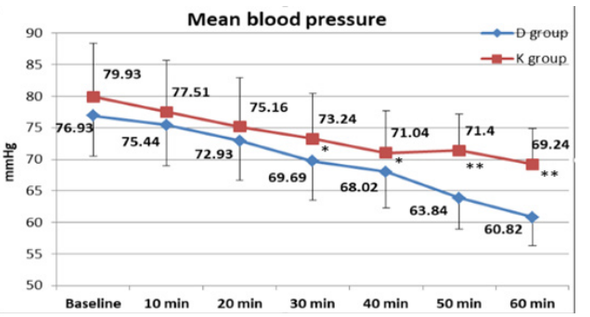

Fig. 2 : Comparison between D group and K group regarding mean blood pressure.Data are presented as mean ± SD and range. Lines represent mean values and error bars are SD.

Sedation score

The MOAA/S scores were significantly lower in group D at 10, 20 and 30 minutes after the administration of the drug compared with group K (Table 1).

Table 1: Comparison between D group and K group regarding sedation score

Sedation score	D group No. = 45	K group No. = 45	Test value•	*P-value*
10 min	4 (4-5) 4 - 5	5 (4-5) 4 - 6	4.226	<0.001**
20 min	3 (3-4) 2 - 4	4 (3-4) 3 - 5	3.357	0.001**
30 min	1 (1-2) 1 - 2	2 (1-2) 1 - 2	3.596	<0.001**

Data are presented as median (IQR). *P-value* < 0.05 is considered statistically significant.

Child parent separation score

Parent separation score for group D was statistically significant at 10 and 20 mins of drug administration with no statistically significant difference at 30 minutes of drug administration (Table 2).

Table 2: Comparison between D group and K group regarding patient separation score

Patient separation score	K group No. = 45	D group No. = 45	Test value•	*P-value*
10 min	2 (2-3) 2 - 3	3 (2-3) 2 - 3	2.953	0.003*
20 min	1 (1-2) 1 - 2	2 (1-2) 1 - 2	2.516	0.012*
30 min	1 (1-1) 1 - 2	1 (1-2) 1 - 2	1.572	0.116

Data are presented as median (IQR). **P-value* < 0.05 is considered statistically significant, *P value* >0.05 is considered non significant.

Sedation satisfaction

A greater number of children in group D achieved satisfactory sedation of 91.1% when compared with group K (75.6%), which was statistically significant (0.048) (Table 3).

Table 3: Comparison between D group and K group regarding patient sedation satisfaction

Patient sedation satisfaction	D group No. = 45		K group No. = 45		Test value•	*P-value*
Satisfactory	41	91.1%	34	75.6%	3.920	0.048*
Unsatisfactory	4	8.9%	11	24.4%		

Data are presented as median (IQR). *P-value* < 0.05 is considered statistically significant.

Adverse effects

The incidence of shivering was significantly higher in group k than in group D ($P < 0.05$). On the other hand, postoperative nausea and vomiting (PONV) showed no statistically significant difference between the two groups ($P > 0.05$), other side effects were not noticed on the study patients.

Table 4 : Comparison between D group and K group regarding Adverse Effects

Adverse Effects	D group No. = 45		K group No. = 45		Test value•	*P-value*
Shivering	5	11.1%	14	31.1%	5.404	0.020*
PONV	2	4.4%	4	8.9%	0.714	0.398

Data are presented as median (IQR). *P-value* < 0.05 is considered statistically significant. PONV: Postoperative nausea and vomiting.

DISCUSSION

Results of the present study showed that intranasal administration of ketamine 2 mg/kg and dexmedetomidine 1 mcg/kg produced effective and significant sedation, observed more in dexmedetomidine group at 10, 20 and 30 mins after drug administration and maintained until induction of anesthesia.

The recommended doses of I.N dexmedetomidine as a premedication for pediatric patients are 1-4mcg/kg with a duration of action ranging from 120-180 min[7] .In the current study , we used I.N dexmedetomidine in a dose of 1mcg/kg . This was based on previous studies which reported that it was more effective in reaching a fast sedation score with fewer adverse effect. Peak plasma concentration was reached at 47 min with 84% bioavailability. Median time of onset on sedation was 25-40 min.[8] That was the reason for administration of the premedication 30 min. before induction of anesthesia in our study.

Different doses of I.N ketamine ranging from 1-7 mg/kg have been studied , with onset of sedation ranging from 8.7-22.19 min .Higher doses were associated with higher incidence of nausea and vomiting , most likely due to NMDA receptor blockade in the vestibular system[9]. In the current study we used I.N ketamine in a dose of 2 mg/kg as it was found that lower doses produced more sedation than higher doses with less side effects[10].

Dexmedetomidine was more favorable during parental separation at 10 and 20 mins of administration. However, at 30 mins, there was no statistically significant difference between the 2 drugs. Both drugs showed good behavioral response, children were calm during separation from their parents while taking them to OR, and also, parents were highly satisfied by this clinical outcome.

Regarding sedation, results of this study were comparable with El shafeey *et al*.[5], they compared intranasal dexmedetomidine and intranasal ketamine for their efficacy as sedative anxiolytics. They found statistically significant increase in sedation score in children premedicated with dexmedetomidine more than those premedicated with ketamine.

Similar results were observed in another study done by Suvvari and his colleagues[11], they compared intranasal dexmedetomidine 2.5 mcg/kg with intranasal ketamine 5 mg/kg for sedation in children undergoing radiotherapy, the study showed an increase in mean sedation score when using dexmedetomidine in comparison to ketamine.

Another study, published by Natarajan and his colleagues[12] compared intranasal dexmedetomidine, midazolam and ketamine in 4 groups giving the drugs at dose of 1 mcg/kg (D1) and 1.5 mcg/kg (D2), 0.2 mg/kg (M1) and 5 mg/kg (K1), for assessment of their sedative and analgesic properties. 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 ($p > 0.05$).

On the other hand, Gyanesh *et al*.[13] compared intranasal dexmedetomidine 1 mcg/kg versus intranasal ketamine 5 mg/kg as premedication for procedural sedation in children undergoing MRI; they concluded that both ketamine and dexmedetomidine were equally effective in that context, with no significant difference between the two groups.

Also, a study by Arun and his colleagues[14] revealed that intranasal dexmedetomidine in a dose of (1 mcg/kg) is clinically less effective as premedication in older children as compared to ketamine (5 mg/kg) recommending the usage of intransal dexmedetomidine in a higher dose (1.5-2 mcg/kg) for the desired level of sedation.

In another randomized trial by Zanaty and El metainy[15], efficacies of nebulized dexmedetomidine, ketamine, and their combination were compared. No significant difference was found in the ease of parental separation and face mask acceptance in groups where subjects were nebulized with either dexmedetomidine or ketamine alone. The level of sedation was significantly greater in the dexmedetomidine-ketamine combination group.

The current study showed a statistically significant decrease in heart rate and blood pressure in dexmedetomidine group 30 minutes after drug administration and during the intraoperative period when compared to the ketamine group. No significant difference was observed however, at 10 and 20 minutes.

Similarly, Zanaty and El metainy[15] when comparing nebulized dexmedetomidine, ketamine and their combination found that heart rate and mean arterial pressure were significantly lower in dexmedetomidine group.

In addition, Yuen *et al*,[16] compared intranasal dexmedetomidine with oral midazolam as premedication in pediatric anesthesia. They found that preoperative 0.5 and 1 mcg/kg intranasal dexmedetomidine reduced heart rate and blood pressure in healthy children during the first hour after drug administration.

In contrast, Mostafa and Morsy[17] when comparing intranasal dexmedetomidine, midazolam and ketamine in children undergoing bone marrow biopsy and aspirate, found statistically significant changes in heart rate, respiratory rate and systolic blood pressure in each group after 30 mins, they attributed these changes to increased levels of sedation. There methodology differs from ours as they have used I.N ketamine in a higher dose (5mg/kg). This might explain the difference in their outcome.

In the present study, no significant change was observed in SpO2 between both groups. None of the patients in both groups had SpO2 < 95% at any point of time during patient monitoring. Similarly, SpO2 was comparable in a study by Elshafeey and his colleagues[5], comparing intranasal dexmedetomidine and ketamine as pre-operative sedation, and none of the patients had SpO2 < 95% at any point of time.

STUDY LIMITATION

As dexmedetomidine was administered in a similar dose to all study patients between 1 and 8 years of age, this could have possibly influenced the results.

Another study limitation was not using nasal atomizer spray that deposit drug solutions more anteriorly.

CONCLUSION

Intranasal dexmedetomidine and intranasal ketamine can be used effectively and safely as preanesthetic medications in children undergoing surgery under general anesthesia. Both drugs produce effective and favorable sedation levels and acceptable parental separation with superiority of dexmedetomidine in sedation scores. Dexmedetomidine also produces some decrease in heart rate and blood pressure which is favorable during surgery.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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APPENDIX 1

Table 5: Modified Observers Assessment of Alertness/ Sedation Scale (MOAA/S)[6].

Score	Description
1	Does not respond to mild prodding or shaking responds only to painful stimuli.
2	Responds to mild prodding or shaking.
3	Responds only after name is called loudly or repeatedly.
4	Lethargic response to name spoken in normal tone.
5	Appears asleep but responds readily to name spoken in normal tone.
6	Appears alert and awake, responds readily to name spoken in a normal tone.

APPENDIX 2

Table 6: Child Parent Separation Scale[18].

Score	Description	Behavior
1	Patient unafraid, cooperative, or asleep	Excellent
2	Patient slightly fearful and/or crying; quieted with reassurance	Good
3	Patient fearful and crying; not quieted with reassurance	Poor

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