Original Article

A comparative study between intranasal dexmedetomidine and intranasal ketamine as a premedication in paediatric surgeries

Rajalakshmi J, D A[1], Lokesh Kumar K S[2*], Santosh Kumar[3]

[1,2,3]Department of Anesthesiology, Dr B R Ambedkar Medical College, Bangalore, Karnataka, INDIA.
Email: lokesh123@gmail.com, ranijayanth_85@yahoo.co.in, santman1985@rediffmail.com

Abstract

Background: This prospective, randomized, double-blind study was designed to evaluate the use of intranasally administered dexmedetomidine vs intranasal ketamine as a premedication in children undergoing general surgeries **Methods**: 60 children of ASA physical status I and II, between the ages 2 to 8yrs were randomly assigned to 2groups. Group D- Patients received intranasal dexmedetomidine (2µg/kg). Group K- Patients received intranasal ketamine (6mg/kg). At 45 minutes after intranasal dose, sedation, ease of separation and IV cannula acceptance, was evaluated **Results**: The Group K had a median onset of action of 11.67 minswhen compared to Group D of 29.47 mins.57% of children in Group Kbecame significantly asleep when compared to 33% in Group D. (p=0.037). Parental separation was excellent in Group K when compared to Group D. (33.33% vs 10%) (P<0.005). Intravenous cannula acceptance was good in Group Kwhen compared to Group D (60% vs 16%). **Conclusion**: Ketamine (6 mg/kg) via intranasal route is better than dexmedetomidine (2µg/kg), in terms of better sedation, parental separation and IV cannula acceptance.
Keywords: Dexmedetomidine, Ketamine, Premedication, Pediatric.

[*]**Address for Correspondence:**
Dr. Lokesh Kumar K S, Department of Anesthesiology, Dr B R Ambedkar Medical College, Bangalore, Karnataka, INDIA.
Email: lokesh123@gmail.com
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INTRODUCTION

The preoperative period is a stressful event for the majority of the individuals undergoing surgery. This is especially true in the paediatric patients.Fear of physicians, nightmares and post operativebehavioural regression, have all been reported. Inaddition to behavioral manifestations, preoperative anxiety activates the human stress response, leading to increased serum cortisol, epinephrine, and natural killer cell activity.[1] An ideal premedicant should be available in a preparation that is readily accepted by children, should have a relatively rapid and reliable onset, should provide anxiolysis with mild sedative effect. Various drugs have been used as a premedicant in pediatric paients. In our study we chose Dexmedetomidine, a highly selective α2-adrenoreceptor agonist drug and Ketamine, a NMDA receptor antagonist as the premedicants via intranasal route. We chose intranasal route as it had a significant advantage of being non invasive, quicker onset of action, bypasses BBB and relatively less or delayed side effects. Therefore this study was conducted to compare premedicant effects of intranasal dexmedetomidine versus intranasal ketamine. The parameters which will differentiate between the two, will be- better acceptance of the drug by patients, parent separation, sedation prior to induction and intravenous cannulation.

METHODS

This is a prospective, randomized study to determine which is the better drug, between dexmedetomidine and ketamine, given intranasally, as a premedication. This study was conducted at Dr. B.R. Ambedkar Medical College, Bangalore. After obtaining approval from Institutional Ethics Committee and written, informed consent from patient's parents, 60 patients of ASA I and

II aged between 2-8years were enrolled into the study. The exclusion criteria included patients with cardiopulmonary ailments, hepatorenal dysfunction, mental retardation, emergency surgeries, nasal and oral deformities, history of recent nasal bleeding or discharge and allergy or hypersensitivity to Dexmedetomidine or Ketamine. Patients were randomly assigned to two study groups by computer generated random tables. Group D- Patients received intranasal dexmedetomidine (2µg/kg). Group K- Patients received intranasal ketamine (6mg/kg). Children were kept nil per oral for 6 hours prior to surgery. No premedication was given in the wards. Children were kept in holding area in comforting presence of their parents and were connected to all standard monitors. Baseline heart rate, blood pressure and oxygen saturation was measured before premedication. Intranasal dose of the drug was administered after seeking consent from the parents. The solutions were prepared in 2.5 mL syringes. Equal volumes of the prepared solution were then dripped into both nostrils of the patients. The drug was administered with patients in the supine position.Children were constantly observed for heart rate, blood pressure and saturation and the possible side effects like nausea, vomiting and increased salivation. Readings were taken at 10 minutes interval until 45 minutes, when child was separated from parents. At 45 minutes after intranasal dose, sedation, ease of separation and IV cannula acceptance, was evaluated on a four point score scale. The scoring scales[2] that were used are as follows:

Table 1: Scoring scale

Score	Sedation score	Separation score	Intravenous cannula acceptance score
1	Agitated	Poor (crying, clinging)	Poor (terrified, crying)
2	Awake	Fair (crying but not clinging)	Fair (fear of needle, not reassured)
3	Drowsy	Good (whimpers, easily reassured)	Good (slight fear, easily reassured)
4	Asleep	Excellent (easy separation)	Excellent (readily accepts cannula)

Children with scores 3 or 4 will be considered as satisfactory sedation or separation from parents. Scores 1 or 2 will be considered as unsatisfactory sedation or separation. In operation theatre, intravenous cannulation was done before induction of anaesthesia. A four point evaluation system was used to evaluate acceptance of intravenous cannula. Children with score 3 or 4 were taken as satisfactory acceptance while scores 1 or 2 were taken as unsatisfactory acceptance. The pertainingdata were collected by the attending anaesthesiologist in the data collection form and the following were recorded: sedation score, parental separation score, intravenous cannula acceptance scale and hemodynamic parameters like heart rate, SBP, DBP, MAP, RR, $SP0_2$ and side effects. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

In the present study sedation scores and hemodynamics were compared between Dexmedetomidine (Group D) and Ketamine (Group K) by intranasal route. Groups were comparable regarding age, gender, weight and height.(Table 2)

Table 2: Demographic Data

Demographic Data	Group d	Group k	P value
Age(yrs)	4.83±2.12	5.17±1.89	0.523
Gender (m;f)	14:16	15:15	0.796
Weight(kg)	13.87±4.61	15.83±4.80	0.111
Height(cm)	103.57±11.62	106.57±13.22	0.354

All values expressed in mean±SD, except gender expressed as male to female ratio. There was no statistically significant difference between the diagnosis and surgical procedure in the two groups. The ketamine group had a significantly faster onset of action (time from administration of the drug to beginning of drowsiness that is attaining sedation score scale 3.) of 11.67 mins when compared to dexmedetomidine group of 29.47 mins.

Table 3: Intergroup comparison of onset of action based on sedation score scale 3 in minutes

Onset	Group D		Group K	
	No	%	No	%
<10	0	0.0	4	13.3

10-20	0	0.0	26	86.7
21-30	19	63.3	0	0.0
31-40	11	36.7	0	0.0
Total	30	100.0	30	100.0
Mean ± SD	29.47±4.13		11.67±1.81	

Mean onset of action is significantly more in Group D=<0.001**

Table 4 shows all the 17 patients (57%) in ketamine group became asleep while 10 patients (33%) in dexmedetomidine group became asleep, while 13 patients (43%) in ketamine group were drowsy compared to 18 patients (60%) in dexmedetomidine group. 2 patients in dexmedetomidine group remained awake. So patients in ketamine group were more asleep than dexmedetomidine group with p=0.037 which is statistically significant. That means patients in ketamine group were better sedated than patients in dexmedetomidine group.

Table 4: Comparison of Sedation score in two groups of children studied

Sedation score	Group D (n=30)	Group K (n=30)
Agitated	0	0
Awake	2	0
Drowsy	18(60.0%)	13(43.3%)
Asleep	10(33.3%)	17(57.0%)

Table 5 shows 10 patients (33.33%) in ketamine group showed excellent separation compared to 3 patients (10%) in dexmedetomidine group. The separation in14 patients (46.66%) in ketamine group were good when compared to 12 patients (40%) in dexmedetomidine group. The separation in 6 patients (20%) in ketamine were fair when compared to 15 patients (50%) in dexmedetomidine at the time of separation. Ketamine group patients had better parental separation as compared to Dexmedetomidine group patients with P<0.005 which is statistically significant.

Table 5: Comparison of Separation score in two groups of children studied

Separation score	Group D (n=30)	Group K (n=30)
Poor	0	0
Fair	15(50%)	6(20%)
Good	12(40%)	14(46.66%)
Excellent	3(10%)	10(33.33%)

Table 6 shows one patient had excellent intravenous cannula acceptance in ketamine group when compared to 0 patients in dexmedetomidine. 18 patients (60%) had good intravenous cannula acceptance in ketamine group while only 5 patients (16%) in dexmedetomidine group. 11 patients (36.66%) in ketamine group had fair intravenous cannula acceptance while 23 patients (76.66%) in dexmedetomidine showed the same. The intravenous cannula acceptance was poor in 2 patients with dexmedetomidine while none of the patients with ketamine showed poor acceptance. Ketamine group patients had better acceptance of intravenous cannula with p<0.001 which is statistically significant as compared to Dexmedetomidine group patients.

Table 6: Comparison of Intravenous Cannula Acceptance scale in two groups of children studied

Intravenous Cannula Acceptance scale	Group D (n=30)	Group K (n=30)
Poor	2(6.7%)	0
Fair	23(76.66%)	11(33.66%)
Good	5(16%)	18(60%)
Excellent	0	1(3.3%)

The hemodynamic parameters taken into consideration were the blood pressure (systolic, diastolic and the mean), heart rate, respiratory rate and saturation. Statistical evaluation showed modest change from the baseline but a significant difference in HR and SBP between the groups after the respective drug administration starting at 10 minutes onwards until 45minutes. This statistical significance was due to the decrease in the heart rate caused by dexmedetomidine and increase in the heart rate caused by ketamine. Out of 30 patients 2 patients of dexmedetomidine group developed nausea and vomiting, that is around 6.7%. In the ketamine group, out of 30 patients, 4 patients developed vomiting, that is around 13.3%, 5 patients developed salivation that is around

16.7%. Two patients of the ketamine group developed tachycardia and one developed hypertension, and one patient developed involuntary movements. However none of the patients developed respiratory depression amongst the two groups.

DISCUSSION

Premedication is aimed to relieve anxiety, apprehension, fear and resistance to anaesthesia. We observed in our study that intranasal route had a significant advantage of noninvasive, quicker onset of action and relatively less or delayed side effects. The effectiveness of the premedicant was assessed mainly by sedation, parental separation and IV cannula acceptance scores. We observed that ketamine was superior to dexmedetomidine by having a faster onset of action (11.67±1.81 vs 29.47±4.13 minutes). More patients were found to be asleep in ketamine group (57% vs 33.3%). Better parental separation was seen after intranasal ketamine administration (33.33% vs 10%). The intravenous cannula acceptance was good in ketamine group (60% vs 16%). Mohamed .A.Daabiss*et al*[3] compared oral dexmedetomidine with oral combination of ketamine-midazolam and found that the ketamine-midazolam group had an earlier onset of action (18.3 minutes) compared to dexmedetomidine (24.5 minutes) Weksler, N *et al*[4] in his study showed that out of 86 children who were administered intranasal ketamine at 6mg/kg, 48 patients had excellent sedation, adequate sedation was found in 19 patients. Similarly, in our study, after ketamine administration, 17(57%) patients were found to be asleep and 13(43.3%) were drowsy and after dexmedetomidine administration 10(33.3%) patients were asleep, 18(60%) were drowsy. Yuen *et al* [5] studied the effects of intranasal dexmedetomidine in various doses such as 0.5, 1 and 1.5µg/kg and inferred that the doses of 1 and 1.5µg/kg produced significant sedation in healthy volunteers but clinical sedation required for painful procedure could not be achieved. They opined that dexmedetomidine produces sedation similar to natural sleep and so patients were easily aroused at the time of IV cannulationand 2 remained awake which was statistically significant. In our study the hemodynamic parameters such as HR, SBP, DBP and MAP in intranasal ketamine group showed a significant increase. HR increased by 10% and increase in BP was 14%. It was taken as, any increase in BP above 20% of baseline as hypertension and HR by more than 140bpm in the age group of 2-5years and more than 120bpm in the age group of 6-8years as tachycardia[6]. In our study, only 2 patients showed tachycardia and 1 patient showed hypertension according to the above study criteria. The rise in hemodynamics could be attributed to the centrally mediated sympathomimetic response. Jeffrey P. Morray *et al* [7] showed there was statistically significant but clinically minor increase in heart rate, mean arterial pressure after ketamine was administered. They explained that cardiovascular effects to ketamine were due to direct effects on the heart rate and peripheral vascular resistance and indirect effects mediated through centrally induced increases in sympathetic activity which is believed to be responsible for the increase in heart rate and myocardial contractility. Yuen *et al* [4] in his study showed that there was no significant reduction in SpO_2 below 95% for dexmedetomidine with 1 and 1.5µg/kg. In the present study SpO_2 and respiratory rate did not show any significant changes from baseline in both the groups. The side effects found in our study, in both groups, included minimal amount of vomiting and salivation which did not require any intervention. In addition ketamine group had 2 patients with tachycardia and 1 patient with hypertension and 1 patient showed involuntary movements. However these side effects were statistically insignificant and no medical interventions were required. Diaz JH *et al*[8] in a double blinded controlled study compared intranasal ketamine with placebo and showed that there was no significant difference in vomiting between the two groups. Therefore in our study, premedication with intranasal dexmedetomidine and intranasal ketamine showed that onset of action is faster with ketamine group .The sedation, parental separation and IV cannula acceptance is also better with the ketamine group. The statistically significant differences in hemodynamic parameters were of minor importance clinically. Also ketamine was more cost effective when compared to dexmedetomidine.

CONCLUSION

Both ketamine and dexmedetomidine as premedicant, provided adequate sedation with minimal side effects in paediatric patients. But ketamine when given in a dose of 6 mg/kg via intranasal route is better than that of dexmedetomidine given in a dose of 2µg/kg, in terms of better sedation, parental separation, IV cannula acceptance and is also more economical when compared to dexmedetomidine.

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