

COMPARATIVE EFFICACY OF NEBULISED DEXMEDETOMIDINE, KETAMINE AND MIDAZOLAM FOR PREOPERATIVE PREMEDICATION IN CHILDREN UNDERGOING GENERAL ANAESTHESIA: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Background: Preoperative anxiety and poor cooperation are common challenges in children undergoing surgery. An effective premedicant should provide adequate sedation and anxiolysis while maintaining haemodynamic stability, facilitating smooth mask acceptance, and allowing rapid recovery. Nebulised administration offers a non-invasive alternative to conventional routes of drug administration. **Aim:** To compare the efficacy and safety of nebulised dexmedetomidine, ketamine, and midazolam as preoperative premedicants in children undergoing general anaesthesia. **Materials and Methods:** This prospective, randomized, double-blind, three-arm comparative study included 160 children undergoing elective surgery under general anaesthesia. Patients received nebulised dexmedetomidine 2 µg/kg, ketamine 2 mg/kg, or midazolam 0.2 mg/kg approximately 30 minutes before induction. Sedation was assessed using the Ramsay Sedation Scale. Parental separation anxiety, mask acceptance, recovery time, emergence agitation, and adverse events were also assessed. **Results:** Baseline demographic characteristics were comparable among the three groups. At 30 minutes, the median Ramsay Sedation Score was 3 in the dexmedetomidine and ketamine groups and 4 in the midazolam group, with a statistically significant difference between groups ($p=0.04$). Dexmedetomidine produced significantly better parental separation and mask acceptance from 10 minutes onward. Mean recovery time was significantly shorter with dexmedetomidine (21.1 ± 3.4 minutes) compared with midazolam (30.8 ± 4.9 minutes) and ketamine (29.9 ± 4.3 minutes; $p<0.001$). Emergence agitation was also significantly lower with dexmedetomidine ($p<0.001$). Nausea and vomiting were more frequent with ketamine than with dexmedetomidine or midazolam ($p=0.032$). **Conclusion:** Nebulised dexmedetomidine provided a favourable overall profile of sedation, anxiolysis, cooperation, rapid recovery, and low adverse-event burden. Although midazolam produced slightly deeper sedation at 30 minutes, dexmedetomidine provided more predictable and clinically useful sedation with better perioperative recovery.

INTRODUCTION

Preoperative anxiety is common in children undergoing surgery and may make parental separation, intravenous cannulation, and induction of anaesthesia difficult. A stressful induction may also contribute to emergence agitation and postoperative

behavioural disturbances.^[1] Therefore, an ideal paediatric premedicant should provide adequate sedation and anxiolysis without causing excessive respiratory or cardiovascular depression, while also allowing smooth induction and rapid recovery.^[2] Midazolam has traditionally been used for paediatric premedication because of its anxiolytic and sedative

properties, but variable response and paradoxical agitation can occur.^[3] Ketamine provides sedation with preservation of airway reflexes but may be associated with increased secretions, nausea, vomiting, and emergence reactions.^[4] Dexmedetomidine, a selective α_2 -adrenergic agonist, produces a more cooperative, sleep-like form of sedation and has attracted increasing interest in paediatric anaesthesia.^[5]

Nebulization provides a non-invasive route of administration that can be particularly useful in children who are anxious about injections or oral medications. Previous randomized studies have reported that nebulised dexmedetomidine can provide satisfactory sedation, smoother parental separation, and better mask acceptance compared with other commonly used agents. Abdel-Ghaffar et al. demonstrated a favourable overall profile of nebulised dexmedetomidine compared with ketamine and midazolam in preschool children, while Singariya et al. also reported better sedation and parental separation with dexmedetomidine compared with ketamine.^[6,7]

The present study was therefore undertaken to compare selected clinically relevant outcomes of nebulized dexmedetomidine, ketamine, and midazolam, with particular emphasis on sedation, parental separation, mask acceptance, recovery, emergence agitation, and adverse effects.

Aim and Objectives

Aim

1. To compare the efficacy and safety of nebulized dexmedetomidine, ketamine, and midazolam as preoperative premedicants in paediatric patients undergoing general anaesthesia.

Objectives

1. To compare the level of sedation produced by the three drugs.
2. To compare parental separation anxiety and mask acceptance.
3. To compare recovery time and emergence agitation.
4. To compare the incidence of adverse effects among the three groups.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, randomized, double-blind, three-arm comparative study conducted in the Department of Anaesthesiology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, over a period of 24 months from January 2024 to January 2026. Institutional Ethical Committee approval was obtained, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study Population

The study included paediatric patients aged 2–10 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, who

were scheduled for elective surgery requiring general anaesthesia.

Parents of patients selected for the study were explained in detail about the drugs, its effects, side effects and informed consent was taken. All children underwent a routine pre-anaesthetic check-up. This included a detailed history, physical examination, and baseline investigations required for surgery were done like haemogram, renal function tests, coagulation profile, blood glucose and viral markers. Parents were instructed about preoperative fasting: 8 hours for solids/heavy or fatty meal, 6 hours for semi solids/light meal or infant formula, 4 hours for breast milk and 2 hours for clear liquids as per the Nil Per Oral (NPO) guidelines. Children with parental refusal, known drug allergy, significant hepatic, renal or respiratory disease, significant congenital or acquired cardiac disease, raised intracranial or intraocular pressure, or developmental impairment affecting behavioral assessment were excluded.

Study Groups

For the analysis, 160 children were included and distributed into three groups:

- Dexmedetomidine group: n=54; nebulized dexmedetomidine 2 μ g/kg
- Ketamine group: n=53; nebulized ketamine 2 mg/kg
- Midazolam group: n=53; nebulized midazolam 0.2 mg/kg

The study drugs were diluted in 3 mL of 0.9% normal saline and administered using a jet nebulizer approximately 30 minutes before induction of general anaesthesia.

After nebulization, children were monitored in the preoperative area and shifted to the operating room approximately 30 minutes later. Standard monitoring was continued, and intravenous access was secured. Children were preoxygenated with 100% oxygen for 3 minutes and received glycopyrrolate 0.005 mg/kg IV, fentanyl 2 mcg/kg IV, followed by induction with propofol 2 mg/kg IV. After adequate ventilation and depth of anaesthesia was confirmed, Atracurium 0.5 mg/kg IV followed by maintenance dose of 0.1 mg/kg IV was administered for neuromuscular blockade. The airway was secured with an appropriately sized device, and anaesthesia was maintained with oxygen/air or oxygen/nitrous oxide and sevoflurane/isoflurane. Analgesia and antiemetic prophylaxis were provided with paracetamol (7.5 mg-15 mg/kg body weight IV) and ondansetron 0.1 mg/kg IV, respectively. At the end of surgery, neuromuscular blockade was reversed with neostigmine (0.05 mg/kg IV) and glycopyrrolate (0.01 mg/kg IV), followed by extubation after fulfilling standard criteria. Children were then transferred to PACU for monitoring of vital signs, recovery, emergence agitation, and other perioperative adverse events.

The study protocol used simple randomization with sealed opaque envelopes, and the parent and outcome assessor were blinded to group allocation.

Outcome Assessment

Sedation was assessed using the Ramsay Sedation Scale (RSS) at baseline and at 5, 10, 15, 20, 25, and 30 minutes following nebulization. Parental separation anxiety and mask acceptance were assessed using standardized behavioral scales. Recovery time, emergence agitation, and adverse events were recorded during the postoperative period.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Categorical variables were expressed as frequencies

and percentages. The Kruskal–Wallis test was used for ordinal outcomes such as sedation, parental separation, mask acceptance, and emergence agitation, while appropriate parametric or categorical tests were used for continuous and categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 160 children were included in the final analysis: 54 in the dexmedetomidine group, 53 in the ketamine group, and 53 in the midazolam group. The three groups were comparable with respect to age, sex, and body weight.

Table 1: Baseline Demographic Characteristics

Variable	Dexmedetomidine (n=54)	Ketamine (n=53)	Midazolam (n=53)	p-value
Age (years), Mean $\pm$ SD	5.74 $\pm$ 2.62	6.30 $\pm$ 2.72	6.40 $\pm$ 2.35	0.363
Female, n (%)	27 (50.0)	27 (50.9)	26 (49.1)	0.99
Male, n (%)	27 (50.0)	26 (49.1)	27 (50.9)	
Weight (kg), Mean $\pm$ SD	21.13 $\pm$ 7.09	22.60 $\pm$ 7.34	22.60 $\pm$ 6.12	0.48

The groups were well matched at baseline, with no statistically significant differences in age, gender, or body weight.

Table 2: Sedation Score at 30 Minutes

Group	Ramsay Sedation Score Median (IQR)	Mean $\pm$ SD	p-value
Dexmedetomidine	3 (3–4)	3.41 $\pm$ 0.72	0.04*
Ketamine	3 (3–3)	3.29 $\pm$ 0.48	
Midazolam	4 (3–4)	3.62 $\pm$ 0.61	

*Kruskal–Wallis test.

At 30 minutes, midazolam produced the highest median sedation score. However, the difference in score should be interpreted in the context of the desired level of paediatric premedication, where

excessively deep sedation may not necessarily provide better clinical cooperation. Dexmedetomidine produced a more predictable level of sedation without excessive depth.

Table 3: Parental Separation Anxiety at Selected Time Points

Time	Dexmedetomidine Mean $\pm$ SD	Ketamine Mean $\pm$ SD	Midazolam Mean $\pm$ SD	p-value
Baseline	3.05 $\pm$ 0.82	3.10 $\pm$ 0.79	3.08 $\pm$ 0.81	0.92
5 min	2.32 $\pm$ 0.76	2.48 $\pm$ 0.81	2.51 $\pm$ 0.83	0.18
10 min	1.89 $\pm$ 0.69	2.15 $\pm$ 0.74	2.31 $\pm$ 0.81	0.03*
15 min	1.78 $\pm$ 0.63	2.05 $\pm$ 0.71	2.22 $\pm$ 0.77	0.01*
20 min	1.60 $\pm$ 0.61	1.98 $\pm$ 0.69	2.12 $\pm$ 0.73	0.02*
25 min	1.46 $\pm$ 0.58	1.91 $\pm$ 0.64	2.03 $\pm$ 0.68	$<0.001^*$
30 min	1.52 $\pm$ 0.61	1.98 $\pm$ 0.66	2.14 $\pm$ 0.73	$<0.001^*$

*Kruskal–Wallis test. Lower scores indicate better parental separation.

Parental separation anxiety was similar at baseline but progressively decreased in all groups. Dexmedetomidine produced significantly lower anxiety scores from 10 minutes onward, with the greatest difference observed at 30 minutes.

Table 4: Comparison of Mask Acceptance Scores during Induction of Anaesthesia

Time Point	Group	MAS – Median (IQR)	Mean $\pm$ SD	p-value [‡]
0 minute	Dexmedetomidine (n = 54)	3 (2–3)	2.72 $\pm$ 0.61	0.88
	Ketamine (n = 53)	3 (2–3)	2.78 $\pm$ 0.64	
	Midazolam (n = 53)	3 (2–3)	2.75 $\pm$ 0.62	
5 minutes	Dexmedetomidine (n = 54)	2 (1–2)	1.96 $\pm$ 0.58	0.09
	Ketamine (n = 53)	2 (1–2)	2.12 $\pm$ 0.61	
	Midazolam (n = 53)	2 (1–3)	2.24 $\pm$ 0.66	
10 minutes	Dexmedetomidine (n = 54)	1 (1–2)	1.48 $\pm$ 0.51	0.04*
	Ketamine (n = 53)	1 (1–2)	1.74 $\pm$ 0.56	
	Midazolam (n = 53)	1 (1–2)	1.81 $\pm$ 0.59	

15 minutes	Dexmedetomidine (n = 54)	1 (1–1)	1.29 ± 0.46	0.01*
	Ketamine (n = 53)	1 (1–2)	1.58 ± 0.53	
	Midazolam (n = 53)	1 (1–2)	1.67 ± 0.55	
20 minutes	Dexmedetomidine (n = 54)	1 (1–1)	1.26 ± 0.44	0.02*
	Ketamine (n = 53)	1 (1–2)	1.56 ± 0.52	
	Midazolam (n = 53)	1 (1–2)	1.65 ± 0.53	
25 minutes	Dexmedetomidine (n = 54)	1 (1–1)	1.22 ± 0.41	<0.001*
	Ketamine (n = 53)	1 (1–2)	1.54 ± 0.49	
	Midazolam (n = 53)	1 (1–2)	1.63 ± 0.52	
30 minutes	Dexmedetomidine (n = 54)	1 (1–1)	1.26 ± 0.44	<0.001*
	Ketamine (n = 53)	1 (1–2)	1.57 ± 0.51	
	Midazolam (n = 53)	1 (1–2)	1.69 ± 0.54	

Kruskal–Wallis test; * statistically significant.

At baseline, mask acceptance scores were comparable among the three groups, with a median score of 3 (IQR 2–3) in each group ($p = 0.88$). Differences became apparent from 10 minutes onward, with dexmedetomidine showing consistently lower mean scores than ketamine and midazolam. At 15 minutes, the mean scores were 1.29 ± 0.46 , 1.58 ± 0.53 , and 1.67 ± 0.55 , respectively ($p = 0.01$). This difference persisted at 20 minutes ($p = 0.02$), 25 minutes ($p < 0.001$), and 30 minutes ($p < 0.001$). Since lower MAS scores indicate smoother cooperation during induction, dexmedetomidine demonstrated better mask acceptance over time.

Table 5: Recovery Time and Emergence Agitation

Outcome	Dexmedetomidine	Ketamine	Midazolam	p-value
Recovery time (min), Mean ± SD	21.1 ± 3.4	29.9 ± 4.3	30.8 ± 4.9	<0.001
Emergence agitation, Median (IQR)	1 (1–2)	4 (3–4)	3 (2–3)	<0.001

Dexmedetomidine was associated with significantly faster recovery and markedly lower emergence agitation compared with both ketamine and midazolam.

Table 6: Adverse Events

Adverse Event	Dexmedetomidine (n=54)	Midazolam (n=53)	Ketamine (n=53)	p-value
Bradycardia	2 (3.7%)	1 (1.9%)	0 (0.0%)	0.061
Hypotension	1 (1.9%)	1 (1.9%)	0 (0.0%)	0.118
Desaturation	1 (1.9%)	1 (1.9%)	2 (3.8%)	0.812
Nausea/Vomiting	0 (0.0%)	2 (3.8%)	4 (7.5%)	0.032*

*Statistically significant.

Adverse events were generally uncommon across all three groups. Bradycardia was reported in 2 (3.7%) patients in the dexmedetomidine group and 1 (1.9%) patient in the midazolam group, with no cases in the ketamine group, although the difference was not statistically significant ($p = 0.061$). Hypotension occurred in 1 (1.9%) patient each in the

dexmedetomidine and midazolam groups and was absent in the ketamine group ($p = 0.118$). Desaturation was infrequent and comparable among the groups ($p = 0.812$). Nausea/vomiting was significantly more common in the ketamine group (7.5%) compared with midazolam (3.8%) and dexmedetomidine (0%), with $p = 0.032$.

DISCUSSION

The present study compared three commonly used nebulized premedicants in children undergoing general anaesthesia. The major finding was that although all three agents produced clinically acceptable sedation, dexmedetomidine provided the most balanced overall profile, particularly with regard to parental separation, mask acceptance, recovery, emergence agitation, and adverse effects. At 30 minutes, midazolam produced the highest median sedation score, while dexmedetomidine and ketamine had a median score of 3. The slightly deeper sedation with midazolam does not necessarily indicate superior premedication because the clinical goal is controlled and cooperative sedation rather than maximal sedation.^[8] Previous research has similarly shown that nebulised dexmedetomidine provides reliable sedation without excessive depth.

Abdel-Ghaffar et al. found dexmedetomidine to be an effective alternative to ketamine and midazolam in preschool children,^[6] while Anupriya and Kurhekar demonstrated that nebulised dexmedetomidine at 2–3 µg/kg provides effective preoperative sedation, with the higher dose particularly improving parental separation and mask acceptance in younger children.^[9]

A clear advantage of dexmedetomidine in the present study was its effect on parental separation. Anxiety scores were comparable at baseline but became significantly lower with dexmedetomidine from 10 minutes onward. This finding is consistent with previous randomized studies. Singariya et al. reported better parental separation and sedation with nebulised dexmedetomidine compared with ketamine, while Shereef et al. found that nebulised dexmedetomidine was effective in reducing parental separation anxiety and improving mask acceptance in preschool children.^[7,10]

Mask acceptance is particularly important because good premedication should translate into smoother induction rather than simply producing sleep. In the present study, dexmedetomidine produced better mask acceptance from 10 minutes onward, with the difference becoming highly significant by 30 minutes. Similar observations have been reported by Abdel-Ghaffar et al., Zanaty and El-Metainy, who demonstrated favourable pre-induction cooperation with nebulised dexmedetomidine.^[6,11]

Recovery time was another important difference. Children receiving dexmedetomidine recovered in 21.1 ± 3.4 minutes compared with approximately 30 minutes in both comparator groups. Faster recovery is particularly relevant for short and day-care procedures because it can facilitate earlier discharge and reduce the duration of postoperative observation. The lower emergence agitation score with dexmedetomidine further strengthens this finding. Previous paediatric studies have also demonstrated reduced emergence agitation with dexmedetomidine compared with other sedative agents.^[12,13]

The adverse-event profile was generally favourable across all three groups. Mild bradycardia and hypotension were observed with dexmedetomidine but were uncommon. Desaturation was comparable among the groups. In contrast, nausea and vomiting were significantly more frequent with ketamine. These findings are consistent with the known pharmacological profile of ketamine and with previous comparative studies in children. Singariya et al. reported comparable overall safety while demonstrating favourable sedation and cooperation with dexmedetomidine.^[7]

Baseline mask acceptance was comparable among the three groups (median 3, IQR 2–3; $p = 0.88$), but scores progressively improved after premedication. From 10 minutes onward, dexmedetomidine showed significantly lower scores than ketamine and midazolam. At 15 minutes, scores were 1.29 ± 0.46 , 1.58 ± 0.53 , and 1.67 ± 0.55 in the dexmedetomidine, ketamine, and midazolam groups, respectively ($p = 0.01$), and at 30 minutes were 1.26 ± 0.44 , 1.57 ± 0.51 , and 1.69 ± 0.54 , respectively ($p < 0.001$). Although both ketamine and midazolam improved mask acceptance, ketamine showed an intermediate effect, while midazolam had comparatively higher scores. Overall, dexmedetomidine provided the best and most consistent mask acceptance and cooperation during induction. Comparable findings were reported by Zanaty et al. who showed improved cooperation scores with nebulised dexmedetomidine compared with ketamine.^[11] Similarly, Anupriya et al. observed better acceptance with dexmedetomidine than with lower doses or alternative agents.^[9] Improved mask acceptance is clinically advantageous because it facilitates smoother induction, reduces the need for restraint, and minimizes psychological trauma.

The findings also support the use of nebulisation as a practical route for paediatric premedication. Nebulisation avoids the distress associated with

injections and may be more acceptable than oral or intranasal administration in some children. Previous randomized studies have demonstrated that nebulised dexmedetomidine can provide satisfactory sedation while maintaining oxygenation and acceptable haemodynamic stability.^[12,14]

Overall, the results suggest that the quality of paediatric premedication should not be judged solely by sedation depth. A clinically useful premedicant should provide a calm but cooperative child, good parental separation, satisfactory mask acceptance, stable physiological parameters, rapid recovery, and minimal adverse effects. In this respect, dexmedetomidine demonstrated the most favourable balance among the three agents.

Strengths of the Study

The major strength of this study is its prospective randomized double-blind comparative design with three active treatment groups. The groups were well matched for age, sex, and weight, reducing the likelihood of demographic confounding. The study also assessed clinically meaningful outcomes beyond sedation alone, including parental separation, mask acceptance, recovery time, emergence agitation, and adverse effects.

Limitations

The study has some limitations. The sample was obtained from a single center, which may limit generalizability to other pediatric populations. Follow-up was limited to the perioperative and early recovery period, so longer-term behavioral outcomes could not be assessed. Behavioral scoring systems, although widely used and clinically relevant, are partly subjective and may be affected by inter-observer variation.

CONCLUSION

Nebulized dexmedetomidine provided a favorable overall profile for pediatric premedication when compared with nebulized ketamine and midazolam. Although midazolam produced slightly deeper sedation at 30 minutes, dexmedetomidine provided better parental separation, superior mask acceptance, faster recovery, less emergence agitation, and a low incidence of adverse effects. These findings suggest that nebulized dexmedetomidine may be a useful non-invasive option for premedication in children undergoing general anaesthesia.

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