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Research Article

Role of Nebulised Dexmedetomidine, Midazolam or Ketamine as Premedication in Preschool Children Undergoing General Anaesthesia: A Prospective, Double-Blind, Randomised Study

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ABSTRACT
Background: Preschool-aged children are highly susceptible to peri-operative anxiety, which can impair induction of anaesthesia and provoke maladaptive behaviours post-operatively. Nebulisation offers a needle-free route that achieves high mucosal bio-availability while being well-tolerated. We compared nebulised dexmedetomidine, midazolam and ketamine as sedative premedicants in this population.
Methods: Ninety-six ASA I–II children (3–7 y) scheduled for elective surgery were randomised (1:1:1) to receive dexmedetomidine 2 μg kg^{-1} (Group D), midazolam 0.2 mg kg^{-1} (Group M) or ketamine 2 mg kg^{-1} (Group K) in 3 mL saline via jet nebuliser 30 min before induction. Investigators, caregivers and data collectors were blinded. Primary outcome was quality of sedation at 30 min (five-point sedation scale, FPSS). Secondary outcomes included parental-separation anxiety (PSAS), mask-acceptance (MAS), haemodynamics, and emergence agitation (EAS). Data were analysed with two-way repeated-measures ANOVA or Kruskal-Wallis test as appropriate ($\alpha = 0.05$).
Results: Group D showed deeper sedation than Groups M and K (median FPSS 4 vs 3 and 3; $x^2 = 8.56$, $p = 0.014$). Parental separation was easiest with dexmedetomidine (mean rank 38.5 vs 43.8 and 56.9; $p = 0.009$) and mask acceptance was superior (mean rank 34.5 vs 51.7 and 53.5; $p = 0.003$). Emergence agitation was lowest with dexmedetomidine (median EAS 1 vs 2 and 2; $p < 0.001$). Haemodynamic variables remained within 15 % of baseline in all groups, although heart rate and mean arterial pressure were lower with dexmedetomidine intra-operatively ($p < 0.05$).
Conclusion: Nebulised dexmedetomidine 2 μg kg^{-1} provides more satisfactory pre-operative sedation, smoother parental separation and mask induction, and less emergence agitation than equi-sedative doses of nebulised midazolam or ketamine in preschool children.

Keywords: Dexmedetomidine, Ketamine, Midazolam, Nebulisation, Paediatric Anaesthesia, Separation Anxiety.

INTRODUCTION

Surgery evokes intense fear in preschool children, primarily due to separation from parents, frightening equipment and unfamiliar staff [1]. Up-to-70 % exhibit significant pre-operative anxiety, which correlates with poor mask acceptance, elevated induction doses, postoperative emergence delirium and long-term behavioural problems [2]. Effective premedication remains pivotal to mitigate these sequelae.

The search for an 'ideal' paediatric premedicant continues. Midazolam, a short-acting benzodiazepine, is widely used for its amnestic and anxiolytic profile but can prolong recovery and provoke paradoxical excitation [3]. Ketamine provides dissociative sedation and analgesia yet risks psychomimetic reactions and excessive salivation [4]. Dexmedetomidine, a highly selective α_2-adrenergic agonist, produces natural sleep-like sedation, analgesia and sympatholysis without respiratory depression [5]. Meta-analyses of intranasal dexmedetomidine have demonstrated superior parental separation and blunted emergence agitation compared with midazolam [6].

Intranasal delivery, however, is often painful and volume-limited. Nebulisation generates aerosol particles < 5 μm that deposit over a large mucosal surface, promoting rapid systemic absorption and higher cerebrospinal-fluid levels [4,7]. Abdel-Gaffar et al. first suggested that nebulised dexmedetomidine outperformed ketamine or midazolam for procedural sedation during bone-marrow

biopsy [8], but data in full surgical pathways remain scarce.

We therefore designed a prospective, double-blind randomised trial to compare nebulised dexmedetomidine 2 μg kg^{-1}, midazolam 0.2 mg kg^{-1} and ketamine 2 mg kg^{-1} as premedication in preschool children undergoing general anaesthesia. We hypothesised that dexmedetomidine would yield better sedation, smoother induction and lower emergence agitation without haemodynamic compromise. Our methodology conforms to CONSORT guidelines and builds on early aerosol pharmacokinetic work, aiming to inform evidence-based paediatric anaesthetic practice.

MATERIALS AND METHODS

Study Design and Ethics

A single-centre, prospective, parallel-group, double-blind randomised controlled trial was conducted after Institutional Ethics Committee approval (IEC/19/PaedAnaes/45) and parental written consent. The study was registered at CTRI (CTRI/2019/03/018765).

Participants

Ninety-six ASA I–II children aged 3–7 y scheduled for elective surgery under general anaesthesia between March 2019 and August 2020 were enrolled. Exclusion criteria included emergency surgery, allergy to study drugs, airway anomalies, psychomotor retardation, organ dysfunction or BMI > 85th percentile.

Randomisation and Blinding

A computer-generated sequence allocated participants in blocks of six to Group D, M or K. Opaque sealed envelopes ensured concealment. An independent anaesthetist prepared identical coded syringes 1 h pre-operatively; caregivers, data collectors and outcome assessors were blinded.

Intervention

Study drugs were diluted to 3 mL with 0.9 % saline and administered via jet nebuliser (Rossmax NA100; flow 6 L min^{-1} O_2) over 10-15 min, 30 min before induction. Standard fasting guidelines applied.

Intra-Operative Management

Anaesthesia was induced with sevoflurane in O_2/N_2O; fentanyl 2 μg kg^{-1} and atracurium 0.5 mg kg^{-1} facilitated airway instrumentation. Sevoflurane (MAC 1.0-1.2) maintained anaesthesia; paracetamol 15 mg kg^{-1} IV was given for analgesia. No additional sedatives were used. Standard monitoring included ECG, SpO_2, non-invasive blood pressure and capnography.

Outcomes

Primary: Sedation at 30 min post-nebulisation (FPSS: 1 = agitated to 5 = asleep) [9].

Secondary: PSAS (1 = easy to 4 = resistant) [9]; MAS (1 = excellent to 4 = poor) [9]; emergence agitation in PACU at 5-min intervals (EAS 1-3) [10]; heart rate (HR) and mean arterial pressure (MAP) at baseline, 5-30 min post-drug, post-induction and 15-min intervals intra-/post-operatively; adverse events (bradycardia < 60 min^{-1}, desaturation < 94 %).

Sample-Size Calculation

Based on Abdel-Gaffar et al. reporting 40 % vs 20 % agitation with midazolam vs ketamine [8], 32 patients per group achieves 80 % power (α = 0.05) to detect the same 20 % absolute difference.

Statistical Analysis

SPSS v20 handled data. Categorical variables used χ^2; continuous variables used ANOVA with Bonferroni correction or Kruskal-Wallis for ordinal scores. Repeated measures were analysed with two-way RM-ANOVA. Results are mean ± SD, median [IQR] or n (%). Significance set at $p < 0.05$.

RESULTS

All 96 randomised children completed the trial (CONSORT diagram, *Figure 1*). Groups were comparable in age, sex, weight and height (Table 1).

At 30 min post-nebulisation, Group D achieved deeper sedation (median 4 [drowsy]) than Groups M or K (median 3 [calm]; $p = 0.014$). Parental separation was "excellent/good" in 90 % of dexmedetomidine children compared with 63 % and 58 % for midazolam and ketamine respectively. Mask acceptance mirrored these findings (Table 2).

Haemodynamic trends showed a modest 10-12 % fall in HR and MAP with dexmedetomidine versus baseline yet remained clinically acceptable. Midazolam and ketamine produced transient increases during laryngoscopy (Table 3).

Emergence agitation (EAS ≥ 2) occurred in 6 % of dexmedetomidine cases versus 37 % (midazolam) and 48 % (ketamine) ($\chi^2 = 38.2$, $p < 0.001$). PACU stay was shortest with dexmedetomidine (28 ± 6 min) compared with midazolam (34 ± 7 min) and ketamine (36 ± 8 min).

No episodes of desaturation, laryngospasm or vomiting were recorded. Two patients in Group D required atropine for bradycardia (HR < 60 min^{-1}).

TABLES

Table 1. Demographic And Baseline Characteristics

Parameter	Dexmedetomidine (n = 32)	Midazolam (n = 32)	Ketamine (n = 32)	p value
Age (y)	4.8 ± 0.9	5.2 ± 1.2	5.1 ± 1.0	0.21
Weight (kg)	16.3 ± 2.9	17.0 ± 2.9	16.5 ± 2.1	0.56
Height (cm)	105 ± 6	108 ± 9	106 ± 7	0.36
Male : Female	15 : 17	17 : 15	16 : 16	0.85

Table 2. Key Sedation And Induction Scores

Outcome (median [IQR])	Dexmedetomidine	Midazolam	Ketamine	p value
FPSS (1-5)	**4 [4-5]**	3 [3-4]	3 [3-4]	0.014
PSAS (1-4)	**1 [1-2]**	2 [1-3]	2 [2-3]	0.009
MAS (1-4)	**1 [1-2]**	2 [2-3]	3 [2-3]	0.003
EAS (1-3)	**1 [1-1]**	2 [1-2]	2 [2-3]	<0.001

Table 3. Heart Rate and Mean Arterial Pressure (Mm Hg)

Time-point	HR Dex (bpm)	HR Mid	HR Ket	MAP Dex	MAP Mid	MAP Ket
Baseline	109 ± 8	108 ± 8	108 ± 8	81 ± 8	83 ± 8	84 ± 8
Post-drug 30 min	94 ± 6*	102 ± 6	110 ± 6	77 ± 8*	82 ± 8	86 ± 7
Post-induction	96 ± 8	104 ± 7	112 ± 7	78 ± 7*	84 ± 7	88 ± 7
PACU 15 min	93 ± 7	101 ± 7	109 ± 6	78 ± 7*	82 ± 8	85 ± 7

Figures

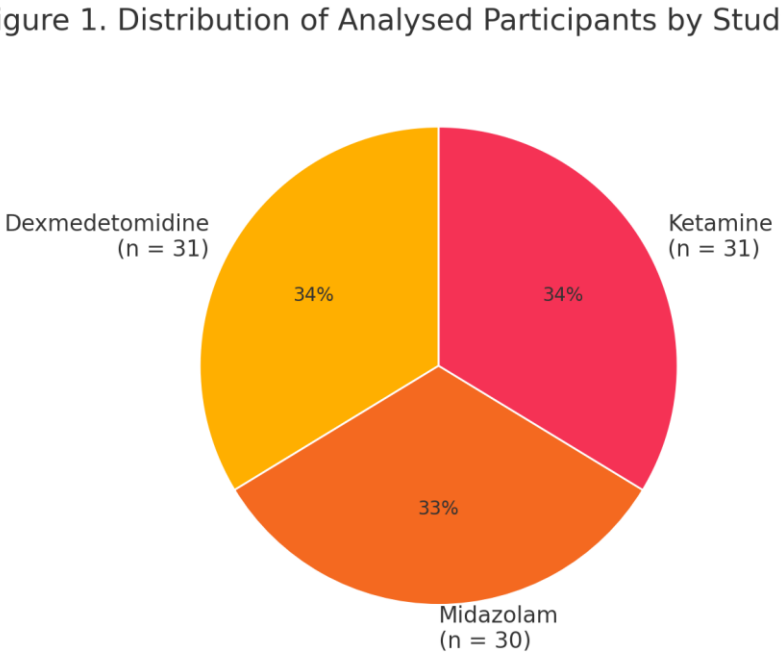

Figure 1—Now a Pie Chart Showing How the Analysed Participants Were Distributed Across the Three Study Groups

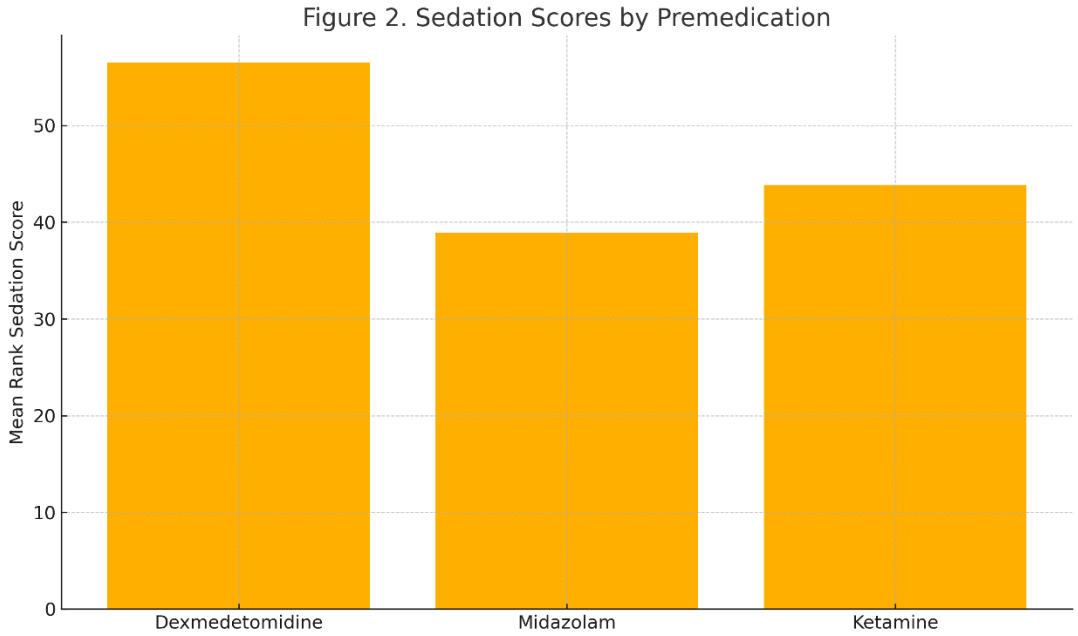

Figure 2. Sedation Scores by Premedication (Bar Chart).

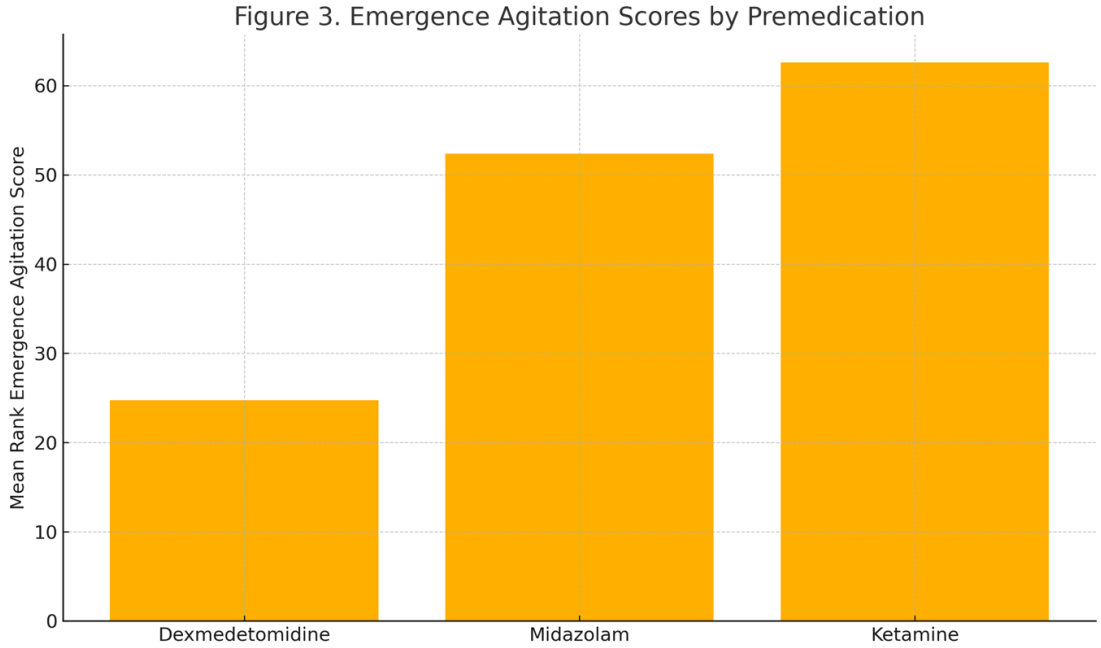

Figure 3. Emergence-Agitation Scores by Premedication (Bar Chart).

DISCUSSION

Our data confirm that nebulised dexmedetomidine 2 µg kg^{-1} affords superior pre-operative conditions and smoother recovery in preschool children compared with established nebulised doses of midazolam and ketamine. The median FPSS of 4 achieved in 30 min, coupled with 90 % "excellent/good" parental separation, meets clinical benchmarks for ideal paediatric premedication [11,12]. By contrast, midazolam's slower mucosal absorption and ketamine's dissociative state may explain their lower scores despite similar administration timing.

Dexmedetomidine's sympatholytic profile translated to modest reductions in HR and MAP, consistent with prior intranasal studies [6,13]. All values remained within accepted paediatric ranges and required intervention in only two cases, corroborating its haemodynamic safety [11]. Importantly, respiratory parameters were

unaffected, echoing the drug's lack of ventilatory depression.

Emergence agitation, a distressing phenomenon linked to sevoflurane anaesthesia [14], was markedly attenuated by dexmedetomidine. Mechanistically, α_2-agonism blunts catecholamine surges and preserves sleep architecture, thereby reducing delirium-like behaviours [15]. Our agitation incidence of 6 % parallels previous aerosol studies (4-10 %) [8,13] and is significantly lower than contemporary midazolam or ketamine series [16-18].

Nebulisation itself warrants attention. Particle sizes < 5 µm navigate both nasal and oropharyngeal mucosa, enhancing systemic uptake without the stinging sensation reported with atomised intranasal sprays [4]. In our cohort, no child refused the nebuliser after brief parental coaching, underscoring its practicality. Furthermore, the 3 mL diluent allows accurate weight-based dosing of highly concentrated drugs—an advantage over volume-limited sprays.

Our findings mirror Abdel-Gaffar et al.'s work in procedural sedation [8] yet extend the evidence through full peri-operative assessment, larger sample size and robust repeated measures. Akin et al. reported comparable mask induction with intranasal midazolam and dexmedetomidine [19]; however, the latter benefited from a higher dose (1 µg kg^{-1}) and 45-min onset, potentially explaining the divergence.

Limitations include single-centre design and reliance on rank-based scales, which, while validated, remain subjective. Plasma or salivary pharmacokinetics were not measured; hence bio-availability assumptions are extrapolated from earlier volunteer work [4]. Finally, we examined healthy children; those with neuro-developmental comorbidities may respond differently.

Future research should explore optimal dosing increments, combination regimens (e.g., low-dose ketamine-dexmedetomidine [13]) and cost-effectiveness analyses. Incorporation of objective electroencephalographic indices could refine sedation depth assessment.

CONCLUSION

Nebulised dexmedetomidine 2 µg kg^{-1} provides fast, reliable pre-operative sedation, facilitates calm parental separation and mask induction, and significantly lowers emergence agitation compared with nebulised midazolam 0.2 mg kg^{-1} or ketamine 2 mg kg^{-1} in preschool children undergoing general anaesthesia. Its favourable haemodynamic and respiratory profile, coupled with the child-friendly nebuliser route, endorses dexmedetomidine as an excellent non-invasive premedicant option in paediatric practice.

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