

Comparison of Intranasal Midazolam versus Dexmedetomidine as Premedication in Paediatric Patients: A Prospective Observational Study

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ABSTRACT

Background and Aims: Preoperative anxiety is common in paediatric patients and frequently precipitates emotional distress, difficult parental separation, and adverse perioperative events. An ideal premedicant should provide rapid, atraumatic sedation without causing respiratory or hemodynamic compromise. While intranasal midazolam is widely used, its acidic formulation often causes nasal irritation and paradoxical agitation. Intranasal dexmedetomidine induces cooperative sedation mimicking natural sleep. This study was undertaken to compare the clinical efficacy of intranasal dexmedetomidine versus intranasal midazolam regarding sedation level, parental separation, and mask acceptance, along with perioperative hemodynamics and adverse effects in paediatric patients.

Methods: This prospective observational study was conducted in the Department of Anaesthesiology at Baby Memorial Hospital, Calicut, Kerala, over a 12-month period. A total of 124 children aged 1–6 years, of ASA physical status I or II, scheduled for elective surgery under general anaesthesia were enrolled. Patients received either intranasal dexmedetomidine 3 mcg/kg (Group A, n = 62) or intranasal midazolam 0.25 mg/kg (Group B, n = 62) using a mucosal atomization device (MAD). Sedation levels (Wilton 5-point scale at 10, 20, and 30 minutes), parental separation reaction (4-point scale at 30 minutes), and face mask acceptance (4-point scale at induction) were evaluated. Secondary endpoints included serial pulse rates, SpO₂, and incidence of nausea and vomiting. Data were analyzed using SPSS version 21.0; categorical data were tested with Chi-square/Fisher's exact tests and continuous variables with Student's t-test or Mann-Whitney U test ($p < 0.05$ considered significant).

Results: At 10 minutes post-administration, most children in both cohorts remained alert ($p = 0.465$). At 20 minutes, midazolam produced earlier calming (59.68% calm vs. 0.00% in Group A; $p < 0.001$). By 30 minutes, dexmedetomidine produced a significantly deeper state of cooperative sedation, with 61.29% classified as drowsy compared to 37.10% with midazolam ($p = 0.041$). Parental separation was rated as "excellent" in 59.68% of children in the dexmedetomidine group versus 37.10% in the midazolam group ($p = 0.028$). Face mask acceptance scores were comparable between groups ($p = 0.211$). Pulse rate and oxygen saturation remained within safe physiological baselines across all time points, with isolated, clinically insignificant hemodynamic variations. Postoperative nausea and vomiting occurred rarely in both groups (3.23% vs. 4.84%; $p = 0.999$).

Conclusion: Intranasal dexmedetomidine at 3 mcg/kg provides superior sedation at 30 minutes and facilitates smoother parental separation compared to intranasal midazolam at 0.25 mg/kg, with equivalent mask acceptance, preserved hemodynamic stability, and no increase in adverse side effects.

Keywords: Paediatric premedication, Intranasal dexmedetomidine, Intranasal midazolam, Parental separation anxiety, Sedation score.

Introduction:

The perioperative environment is uniquely challenging and distressing for paediatric patients. Preoperative anxiety stems from an unfamiliar clinical environment, separation from parents, and fear of needles or bodily harm[1,2]. Untreated anxiety can precipitate intense psychological trauma, uncooperative induction, increased anaesthetic requirements, and adverse behavioral disturbances such as emergence delirium and separation anxiety[2,3]. Therefore, preanaesthetic medication forms a cornerstone of modern paediatric anaesthetic practice.

An ideal premedicant for children should have an atraumatic route of administration, rapid and predictable onset, sufficient duration of action without prolonging recovery, and a low incidence of adverse respiratory or cardio-vascular depression [3,4].

Although intravenous (IV) administration allows rapid drug titration, establishing venous access in an awake, anxious child is technically challenging, painful, and often exacerbates acute distress[3]. Oral administration is painless but carries unpredictable bioavailability, delayed onset, and requires patient cooperation with oral solutions that may taste unpleasant[4].

The intranasal route offers an optimal alternative in paediatric anesthesia. The nasal mucosa possesses rich vascularity and a broad absorptive surface area that allows rapid systemic drug uptake, effectively bypassing hepatic first-pass metabolism[4,5]. Furthermore, the introduction of the Mucosal Atomization Device (MAD) converts liquid medications into a fine microparticulate mist (30–100 μm), maximizing mucosal coverage across the nasal turbinates and olfactory pathways while minimizing the volume of drug lost to the gastrointestinal tract.

Midazolam and dexmedetomidine are two widely utilized premedicants given via the nasal route. Midazolam is a short-acting, water-soluble benzodiazepine that acts as a positive allosteric modulator at GABA A receptor chloride channels, producing rapid anxiolysis, sedation, and anterograde amnesia[8, 9]. However, its parenteral preparation is buffered to an acidic pH (approx. 3.5) to keep the diazepam ring open; on nasal mucosal contact, this often causes a sharp stinging sensation, transient burning, coughing, and paradoxical agitation[9,10].

Dexmedetomidine is a potent and highly selective alpha 2 adrenoceptor agonist (alpha 2:alpha 1 ratio of 1620:1)[11]. It induces sedation by activating presynaptic alpha 2A receptors within the locus coeruleus, reducing central noradrenergic outflow and disinhibiting the ventrolateral preoptic nucleus[11,12]. This produces a distinct state of "cooperative sedation" that mimics non-REM sleep, allowing children to remain easily arousable and interactive while blunting procedural distress, without causing respiratory depression[13,14].

Although multiple studies have explored these agents, observational data reflecting real world clinical workflow and comparative behavioral scales remain valuable. Hence, this prospective observational study was conducted to compare the clinical efficacy of intranasal dexmedetomidine versus intranasal midazolam in facilitating optimal sedation, reducing parental separation anxiety, and easing face mask acceptance in paediatric patients undergoing elective surgical procedures.

Materials and Methods

This prospective observational study was conducted in the Department of Anaesthesiology at Baby Memorial Hospital, Calicut, Kerala, India, over a 12-month period. Ethical clearance was granted by the Institutional Ethics Committee (Ref. No: BMH/Aca/DNB/Anaes/73/2025). Informed written consent was obtained from the parents or legal

guardians of all participating children after thoroughly explaining the study protocol in their native language.

Selection Criteria

Inclusion Criteria: Children aged 1 to 6 years of either sex, weighing between 9 and 25 kg, categorized as American Society of Anesthesiologists (ASA) Physical Status I or II, posted for elective surgical procedures under general anaesthesia.

Exclusion Criteria: Children with active upper respiratory tract infections, rhinorrhea, nasal polyps or nasal structural pathology, known allergy to the study drugs, history of obstructive sleep apnea, central nervous system disorders, neuromuscular diseases, or mental retardation.

Sample Size

The sample size calculation was based on the standard formula:

$$n = (Z(\alpha/2) + Z(\beta))^2 pq / d^2$$

Where,

$Z(\alpha/2)$ is the Z value at an α error,
 $Z(\beta)$ is the Z value at a β error,

p = average percentage of the character = $(p_1 + p_2) / 2$ where p_1 , p_2 are the percentage of the character in each group

$q = 100 - p$,

d = clinically relevant effect size difference = 25%.

Based on reference historical data from Sundaram and Mathian[15], the calculated sample size was 62 patients per group, yielding an overall study cohort of 124 patients.

Methodology & Monitoring

Consecutive sampling was utilized. As this was a prospective observational study, treatment allocation was guided by the clinical decision of the attending anaesthesiologist, resulting in two cohorts:

Group A (n = 62): Received intranasal dexmedetomidine at a dose of 3 mcg/kg.

Group B (n = 62): Received intranasal midazolam at a dose of 0.25 mg/kg.

To mitigate observational bias, the anaesthesiologists who decided the drug allocation did not participate in outcome data collection or statistical analysis.

Following verification of mandatory preoperative fasting guidelines, premedication was drawn using a 2 mL syringe and atomized equally into both nostrils using a Mucosal Atomization Device (MAD) while the child was held comfortably in the parent's lap. Continuous baseline pulse oximetry was instituted.

Parameters Evaluated

1. Sedation Level: Assessed at 10, 20, and 30 minutes following drug administration using the 5-point Wilton scale:

- 1 = Agitated (clinging to parents, crying vigorously)
- 2 = Alert (awake, may whimper, not crying)
- 3 = Calm (sitting/lying comfortably with eyes open)
- 4 = Drowsy (lying comfortably with eyes closed, responds to minor stimulus)
- 5 = Asleep (eyes closed, unrousable to minor stimulus)

2. Parental Separation Anxiety: Scored at 30 minutes during separation at the operating room entrance using a 4-point scale:

- 1 = Excellent (unafraid, cooperative or asleep)
- 2 = Good (slightly afraid / crying, quiets with reassurance)
- 3 = Fair (moderately afraid/crying, does not quiet with reassurance)

○ 4 = Poor (crying vigorously, requires physical restraint)

3. Face Mask Acceptance: Scored during inhalational mask application at the time of induction using a 4-point scale:

- 1 = Excellent (calm, cooperative)
- 2 = Good (cooperative with reassurance)
- 3 = Fair (moderate fear of mask, not easily calmed)
- 4 = Poor (combative, crying)

4. Hemodynamics & Side Effects: Pulse rate and SpO₂ were recorded preoperatively (0, 10, 20, 30 min) and intraoperatively following transfer (0, 5, 10, 15 min). The presence of preoperative or postoperative nausea and vomiting was systematically documented.

Statistical Method

Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0. Continuous demographic and hemodynamic variables were expressed as mean $\pm$ standard deviation (SD) and compared using the Unpaired Student's t-test or Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and evaluated using the Chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

Results

A total of 124 paediatric patients completed the study protocol, with 62 patients in Group A (Dexmedetomidine) and 62 patients in Group B (Midazolam).

1. Demographic Characteristics

Both study cohorts were demographically comparable. The mean age was 3.53 ± 1.76 years in Group A versus 3.29 ± 1.74 years in Group B (p = 0.443). There was no significant difference regarding gender distribution, with males constituting 64.52% (n = 40) in Group A and 61.29% (n = 38) in Group B.

($p = 0.853$) (Table 1).

Table 1: Demographic Profile of the Study Groups

Variable	Group A (Dexmedetomidine, n=62)	Group B (Midazolam, n=62)	p-value
Age (years) (Mean $\pm$ SD)	3.53 $\pm$ 1.76	3.29 $\pm$ 1.74	0.443
Gender (Male/Female)	40 (64.52%) / 22 (35.48%)	38 (61.29%) / 24 (38.71%)	0.853

2. Sedation Scores

- At 10 minutes, the majority of patients in both groups were awake and alert (80.65% in Group A vs. 87.10% in Group B), while mild agitation was seen in 19.35% and 12.90%, respectively ($p = 0.465$).
- At 20 minutes, Group B displayed an earlier onset of sedation: 59.68% ($n = 37$) of children in Group B achieved a "calm" state compared to 0.0% in Group

A, where 96.77% ($n = 60$) remained alert ($p < 0.001$).

- At 30 minutes, Group A demonstrated a deeper quality of sedation: 61.29% ($n = 38$) in Group A progressed to "drowsy" compared to 37.10% ($n = 23$) in Group B. Conversely, 51.61% ($n = 32$) in Group B remained in the "calm" state ($p = 0.041$). Persistent agitation at 30 minutes was minimal and identical in both arms (1.61%, $n = 1$) (Table 2).

Table 2: Comparison of Sedation Scores over Time

Time Point	Sedation Category	Group A (n=62)	Group B (n=62)	p-value
At 10 Minutes	Agitated	12 (19.35%)	8 (12.90%)	0.465
	Alert	50 (80.65%)	54 (87.10%)	
At 20 Minutes	Agitated	2 (3.23%)	2 (3.23%)	<0.001
	Alert	60 (96.77%)	23 (37.10%)	
	Calm	0 (0.00%)	37 (59.68%)	
At 30 Minutes	Agitated	1 (1.61%)	1 (1.61%)	0.041
	Alert	6 (9.68%)	6 (9.68%)	
	Calm	17 (27.42%)	32 (51.61%)	

3. Parental Separation and Mask Acceptance

Parental separation scores at 30 minutes revealed a statistically significant advantage in Group A ($p = 0.028$). Children receiving intranasal dexmedetomidine achieved a significantly higher proportion of "excellent" separation (59.68%, $n = 37$) compared to the midazolam cohort (37.10%, $n = 23$). The

midazolam group showed a predominance of "good" separation (43.55%, $n = 27$) (Table 3). Face mask acceptance during inhalational induction was clinically satisfactory across both cohorts, with no statistically significant difference ($p = 0.211$). Satisfactory acceptance (Score 1 or 2) was observed in 48.39% of Group A and 43.55% of Group B (Table 3).

Table 3: Comparison of Parental Separation and Mask Acceptance Scores

Clinical Endpoint	Category / Score	Group A (n=62)	Group B (n=62)	p-value
Parental Separation Score	Poor (4)	6 (9.68%)	5 (8.06%)	0.028
	Fair (3)	7 (11.29%)	7 (11.29%)	
	Good (2)	12 (19.35%)	27 (43.55%)	
	Excellent (1)	37 (59.68%)	23 (37.10%)	
Mask Acceptance Score	1 (Calm, cooperative)	7 (11.29%)	8 (12.90%)	0.211
	2 (Cooperative with reassurance)	23 (37.10%)	19 (30.65%)	
	3 (Moderate fear)	27 (43.55%)	22 (35.48%)	
	4 (Combative,	5 (8.06%)	13 (20.97%)	

4. Hemodynamics and Adverse Events

Hemodynamic parameters were clinically stable in both cohorts throughout the observation periods (Table 4). Pulse rates showed no significant intergroup difference at baseline (0 min), 10 min, and 20 min preoperatively. At 30 minutes preoperatively, pulse rate was slightly lower in Group A (100.13 ± 6.98 vs. 103.29 ± 6.84 bpm; $p = 0.012$), as well as at 15 minutes intraoperatively (107.24 ± 7.98 vs.

110.65 ± 6.38 bpm; $p = 0.010$). However, neither bradycardia nor hypotension requiring clinical intervention was observed. Peripheral oxygen saturation (SpO₂) remained within normal limits in all subjects, with both cohorts maintaining 100% SpO₂ intraoperatively following mask induction. Postoperative nausea and vomiting occurred rarely, affecting 2 patients (3.23%) in Group A and 3 patients (4.84%) in Group B ($p = 0.999$).

Table 4: Perioperative Hemodynamics and Adverse Events

Parameter	Time Point	Group A (n=62)	Group B (n=62)	p-value
Pulse Rate (bpm)	Pre-op 0 min	104.42 ± 7.64	103.92 ± 7.15	0.707
	Pre-op 10 min	103.19 ± 7.37	103.73 ± 6.69	0.674
	Pre-op 20 min	102.19 ± 6.96	103.40 ± 6.88	0.333
	Pre-op 30 min	100.13 ± 6.98	103.29 ± 6.84	0.012
	Intra-op 0 min	105.63 ± 7.77	106.50 ± 7.65	0.530
	Intra-op 5 min	106.65 ± 7.30	108.34 ± 7.31	0.199
	Intra-op 10 min	107.24 ± 7.98	110.65 ± 6.38	0.010
	Intra-op 15 min	107.24 ± 7.98	110.65 ± 6.38	0.010

		Intra-op 15 min			
Oxygen Saturation (%)	Pre-op 0 min		99.23 ± 0.73	98.94 ± 0.92	0.055
	Pre-op 10 min		99.00 ± 0.63	98.69 ± 0.95	0.036
	Pre-op 20 min		98.97 ± 0.65	98.66 ± 0.97	0.042
	Pre-op 30 min		99.26 ± 0.44	98.65 ± 1.01	<0.001
	Intra-op (5–15 min)		100.00 ± 0.00	100.00 ± 0.00	—
Nausea Vomiting	/	Present / Absent	2 (3.23%) / 60 (96.77%)	3 (4.84%) / 59 (95.16%)	0.999

Discussion

Preoperative anxiety in paediatric patients leads to adverse behavioral reactions during separation and mask induction, and has been correlated with emergence delirium and post-hospitalization regressive behaviors[1,2]. Delivering premedicants via the nasal mucosa using atomization avoids painful injections and minimizes absorption delays associated with the oral route[4,6].

In the present study, intranasal midazolam (0.25 mg/kg) exhibited a more rapid onset of sedation, producing calm behavior in 59.68% of children by 20 minutes compared to none in the dexmedetomidine group. This rapid onset reflects the quick transmucosal uptake and passage across the blood-brain barrier characteristic of midazolam[9,16]. However, by 30 minutes, intranasal dexmedetomidine (3 mcg/kg) produced a significantly deeper and more desirable sedative state, with 61.29 % of patients

classified as drowsy compared to 37.10% in the midazolam group ($p = 0.041$).

These results align closely with the pharmacokinetic profile of dexmedetomidine, which typically requires 25 to 30 minutes to attain peak therapeutic cerebrospinal fluid concentrations following intranasal atomization[13,17]. Sheta et al.[18] previously observed a median onset time of 15 minutes for intranasal midazolam compared to 25 minutes for dexmedetomidine, noting that the depth and quality of sedation favored dexmedetomidine as holding times lengthened. Similar patterns were documented by Yuen et al.[17] and Ghali et al.[19], confirming that dexmedetomidine establishes deeper cooperative sedation without respiratory depression.

Parental separation is a primary benchmark of premedication success. In this trial, dexmedetomidine provided superior parental separation scores, with 59.68% of children exhibiting "excellent" separation compared to 37.10% in the midazolam cohort ($p = 0.028$). This finding is consistent with meta-analyses by Pasin et al.[20] and Fu et al.[21], as well as clinical trials by Akin et al.[22] and Dangi et al.[23], who reported smoother, less traumatic parent-child separation with dexmedetomidine. The difference is attributable to the unique non-REM sleep-like state produced by alpha 2 agonism in the locus coeruleus, whereas midazolam may induce incomplete anxiolysis or transient agitation secondary to nasal stinging[9,10].

During inhalational induction, face mask acceptance scores were satisfactory and statistically comparable between groups (Score 1 or 2: 48.39% in Group A vs. 43.55% in Group B; $p = 0.211$). While some prior investigations reported superior mask compliance with dexmedetomidine[23,24], others noted comparable results when induction was carried out gently[25,26]. The comparable mask acceptance here suggests that once a calm or drowsy state is established, both agents allow an adequate clinical window for inhalational induction.

Both medications preserved perioperative cardiovascular and respiratory stability. Group A exhibited slightly lower pulse rates at 30 minutes preoperatively and 15 minutes intraoperatively, reflecting the expected centrally mediated sympatholytic effect of dexmedetomidine[11,27]. However, these changes were well within age-adjusted physiological thresholds, and no episodes of clinically significant bradycardia or hypotension requiring atropine or fluid boluses occurred. These observations parallel those of Baheti and Toshniwal[28] and Diwan et al.[29], who observed modest, hemodynamically stable decreases in heart rate with intranasal dexmedetomidine. Peripheral oxygenation was well maintained throughout, with no respiratory depression or hypoxia detected in either group, confirming the respiratory safety profile of both regimens[25].

The incidence of nausea and vomiting was minimal in both groups (3.23% vs. 4.84%, $p = 0.999$). This confirms findings by Ericksen et al.[30], showing that intranasal premedication with either drug is well tolerated and does not provoke early emetic symptoms.

Limitations

Study Design:

The observational nature of this trial meant drug selection was based on consultant preference rather than randomized allocation, introducing potential selection bias.

Blinding:

The outcome observers were not blinded to the drug administered, which could introduce detection bias on subjective behavioral scales.

Recovery Outcomes:

Postoperative endpoints such as emergence delirium scores, recovery room length of stay, and long-term behavioral changes were not evaluated.

Conclusion

Intranasal dexmedetomidine at a dose of 3 mcg/kg provides superior sedation at 30 minutes and facilitates smoother, more atraumatic parental separation compared to intranasal midazolam at 0.25 mg/kg in paediatric patients aged 1 to 6 years. Both agents provide comparable face mask acceptance during inhalational induction while maintaining reliable hemodynamic and respiratory stability with minimal adverse events. Intranasal dexmedetomidine is an effective and safe premedicant in paediatric anaesthetic practice when a 30-minute pre-induction window is available.

Conflict of interest: NIL

Financial support: NIL

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