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A COMPARATIVE STUDY OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM AS PRE-ANESTHETIC AGENTS IN PEDIATRIC POPULATION

Anaesthesiology

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ABSTRACT

Background: Preoperative anxiety impacts 50–80% of paediatric surgical patients, resulting in negative consequences, including emerging delirium, heightened postoperative pain, and alterations in behaviour. Effective premedication is essential for anxiolysis, sedation, and a seamless induction. This study evaluated intranasal dexmedetomidine (1 µg/kg) against intranasal midazolam (0.2 mg/kg) as premedication in paediatric patients. **Methods:** This prospective, randomized, double-blind trial included 60 ASA I–II children, aged 2–12 years, scheduled for elective surgery under general anaesthesia. Patients were randomly assigned to Group D (dexmedetomidine) or Group M (midazolam), which were given through the nose 60 minutes before induction. The main outcomes at 60 minutes were sedation (on the Alertness/Sedation scale), anxiety (on a 3-point scale), separation from the parent (on a 3-point scale), and acceptance of the mask (on a 3-point scale). Secondary outcomes were serial hemodynamic measurements (HR, SBP, DBP, MAP, RR, SpO_2) at 0, 15, 30, 45, and 60 minutes, as well as adverse events. The data were examined utilizing an unpaired t-test and chi-square/Fisher's exact test ($p < 0.05$). **Results:** The groups were demographically similar ($p > 0.05$). Dexmedetomidine resulted in considerably improved sedation (2.80 ± 1.03 vs 3.70 ± 0.83, $p = 0.000$), reduced anxiety (1.16 ± 0.37 vs 1.46 ± 0.54, $p = 0.010$), and facilitated separation (1.40 ± 0.49 vs 1.80 ± 0.66, $p = 0.010$). The trend for mask acceptance was superior (1.63 ± 0.61 vs. 1.96 ± 0.76, $p = 0.060$). Categorical distributions indicated a preference for dexmedetomidine in sedation ($p = 0.007$), anxiety ($p = 0.012$), and separation ($p = 0.032$). Hemodynamics exhibited minor, clinically insignificant decreases in Group D (e.g., reduced MAP at 30–60 minutes, $p < 0.05$); no adverse events were reported. **Conclusion:** Intranasal dexmedetomidine 1 µg/kg is more effective than intranasal midazolam 0.2 mg/kg for premedication, providing superior sedation, anxiolysis, and parental separation while ensuring hemodynamic stability and safety.

KEYWORDS

Pre-operative Anxiety, Dexmedetomidine, Intranasal Midazolam

INTRODUCTION

Preoperative anxiety in children undergoing surgery is prevalent, affecting 50–80% of paediatric patients, and poses significant challenges in anaesthesia practice (1). It often manifests as fear, crying, agitation, or resistance during separation from parents and mask induction, leading to increased stress for the child, family, and healthcare team.

Untreated preoperative anxiety is associated with negative perioperative outcomes, such as increased postoperative pain, emergence delirium, maladaptive behavioural changes persisting for weeks to months, extended recovery periods, and heightened healthcare utilization (1,2). Consequently, effective premedication is crucial to mitigate anxiety, ensure smooth parental separation, enhance mask acceptance, promote calm induction, and reduce complications while maintaining safety, particularly regarding respiratory or hemodynamic stability.

Midazolam, a benzodiazepine, is still a common premedicant for children since it works quickly to calm them down, put them to sleep, and make them forget things. Oral midazolam (0.5 mg/kg) is common, but it has drawbacks, including bitter taste causing poor compliance, variable absorption and bioavailability, risk of paradoxical agitation, and potential respiratory depression in susceptible children (3). Intranasal midazolam (0.2 mg/kg) provides a non-invasive alternative with quicker onset through nasal mucosa absorption, avoiding first-pass metabolism, and has been employed effectively for premedication (4).

Dexmedetomidine is a selective α2-adrenergic agonist that acts on the locus coeruleus in the brain to cause sedation that feels like natural sleep. It also reduces anxiety and pain, while keeping airway reflexes intact and causing only mild respiratory depression (5). Intranasal dexmedetomidine (usually 1–2 µg/kg) has good bioavailability (~65%) and works quickly, making it a good choice for premedication. It prevents paradoxical responses that might happen with benzodiazepines and may help with emerging agitation (6).

Meta-analyses and randomized trials comparing intranasal dexmedetomidine with midazolam (often oral) demonstrate advantages for dexmedetomidine, including superior parental separation, deeper sedation, better induction conditions, and lower emergence agitation incidence, with comparable mask acceptance and safety profiles (7,8). Intranasal dexmedetomidine is associated with fewer perioperative respiratory adverse events than intranasal midazolam in specific procedures like tonsillectomy (9). Direct intranasal comparisons are fewer but suggest dexmedetomidine yields better sedation and separation with modest, reversible hemodynamic effects (10,11).

The direct comparisons between intranasal dexmedetomidine (1 µg/kg) and intranasal midazolam (0.2 mg/kg) in general paediatric populations, particularly in resource-constrained environments, are still scarce. Most findings support dexmedetomidine for improved efficacy, although the onset may be delayed. This prospective randomized trial evaluated these medicines in ASA I–II children aged 2–12 years receiving elective surgery under general anaesthesia.

MATERIALS AND METHODS

This prospective, randomized, double-blind, comparative clinical trial was executed in the Department of Anaesthesiology, Government Hospital, Gandhi Nagar, Jammu, from 2021 to 2024. The Institutional Ethics Committee authorized the study procedure, and the parents or guardians of all participants signed a form giving their written approval.

During the study, sixty children, aged 2 to 12 years, with American Society of Anaesthesiologists (ASA) physical status I or II, were enrolled for elective surgery under general anaesthesia. Exclusion criteria encompassed parental refusal of consent, established hypersensitivity to dexmedetomidine or midazolam, nasal congestion or pathology that may hinder intranasal absorption, active upper respiratory tract infection, developmental delay or neurological disorder, obesity (BMI >30 kg/m^2), congenital heart disease, renal/hepatic dysfunction, anticipated difficult airway, or any contraindication to the study medications.

Randomization and Blinding: Patients were randomly divided into

two equal groups of 30 people each using computer-generated random numbers that were sealed in opaque envelopes. Group D got 1 µg/kg of dexmedetomidine through their noses, and Group M got 0.2 mg/kg of midazolam through their noses. An independent anaesthesiologist, who was not engaged in evaluating patients or giving anaesthesia, made the study medicines by mixing dexmedetomidine (100 µg/mL) or midazolam (5 mg/mL) with normal saline to make a total of 1 mL.

The medications were delivered dropwise into each nostril using a 1-mL syringe while the kid was lying down in the preoperative holding area, 60 minutes before the induction of anaesthesia. The observer evaluating results and the anaesthesiologist administering anesthesia were unaware of group assignment.

Standard monitoring (heart rate [HR], non-invasive blood pressure [systolic BP {SBP}, diastolic BP {DBP}, mean arterial pressure {MAP}], respiratory rate [RR], and peripheral oxygen saturation [SpO_2]) began when the patient arrived in the holding area (baseline, t=0) and was recorded at 15, 30, 45, and 60 minutes after premedication. The Alertness/Sedation scale (score 1–5; 1 = deep sleep, unarousable; 5 = awake and alert) was used to measure sedation. A three-point scale was used to measure anxiety: 1 = calm, 2 = uneasy but cooperative, and 3 = highly anxious/crying. There was a 3-point scale for child-parent separation: 1 = simple separation, 2 = hesitant, and 3 = sobbing, requiring restraining. There was a 3-point rating for mask acceptance during induction: 1 = excellent/cooperative; 2 = good/fair; 3 = poor/resists. A blinded observer did all of the tests 60 minutes after the premedication.

Anaesthesia Protocol: General anaesthesia was started using intravenous propofol, fentanyl, and vecuronium. This was followed by endotracheal intubation and maintenance with sevoflurane in a mixture of oxygen and nitrous oxide. During the operation, we kept an eye on and wrote down any changes in blood flow and any problems that came up, such as bradycardia, hypotension, respiratory depression, nausea, and vomiting.

Sample Size and Statistical Analysis: The sample size was established based on previous research indicating disparities in sedation and separation ratings between intranasal dexmedetomidine and midazolam, targeting 80% power and $\alpha = 0.05$, leading to 30 patients per group (considering possible dropouts). For continuous variables, data were shown as mean ± standard deviation, and for categorical variables, as percentages. We used the unpaired t-test to compare continuous data and the chi-square or Fisher's exact test to compare categorical data. A p-value of less than 0.05 was deemed statistically significant. Standard statistical software was used to do the analysis.

RESULTS

A total of 60 children (ASA I-II, aged 2-12 years) undergoing elective surgery under general anaesthesia were randomized into two equal groups (n=30 each). Group D received intranasal dexmedetomidine 1 µg/kg, and Group M received intranasal midazolam 0.2 mg/kg, administered 60 minutes before induction. The groups were comparable at baseline.

Table 1: Demographic and Baseline Hemodynamic Parameters (Mean ± SD)

Parameter	Group D (n=30)	Group M (n=30)	p-value
Age (years)	6.73 ± 3.03	6.48 ± 2.84	0.74
Height (cm)	116.93 ± 18.81	116.83 ± 15.36	0.98
Weight (kg)	21.16 ± 10.80	21.10 ± 6.04	0.97
Heart rate (bpm)	93.13 ± 5.27	92.26 ± 3.92	0.47
SBP (mmHg)	107.86 ± 5.55	108.23 ± 5.95	0.80
DBP (mmHg)	66.86 ± 6.98	65.33 ± 7.09	0.40
Respiratory rate (/min)	16.83 ± 1.82	16.96 ± 1.44	0.75
SpO_2 (%)	98.43 ± 0.62	98.43 ± 0.62	1.00

The two groups were comparable at baseline with respect to demographic and hemodynamic parameters (all $p > 0.05$). Mean age was similar between Group D (6.73 ± 3.03 years) and Group M (6.48 ± 2.84 years, p = 0.74). Height (116.93 ± 18.81 cm vs 116.83 ± 15.36 cm, p = 0.98), weight (21.16 ± 10.80 kg vs 21.10 ± 6.04 kg, p = 0.97), heart rate (93.13 ± 5.27 bpm vs 92.26 ± 3.92 bpm, p = 0.47), systolic blood pressure (107.86 ± 5.55 mmHg vs 108.23 ± 5.95 mmHg, p = 0.80), diastolic blood pressure (66.86 ± 6.98 mmHg vs 65.33 ± 7.09 mmHg, p = 0.40), respiratory rate (16.83 ± 1.82/min vs 16.96 ± 1.44/min, p = 0.75), and SpO_2 (98.43 ± 0.62% in both groups, p = 1.00) showed no statistically significant differences (Table-1).

Table 2: Primary Outcome Scores (Mean ± SD)

Scale	Group D	Group M	p-value
Alertness/Sedation scale	2.80 ± 1.03	3.70 ± 0.83	0.000
Anxiety scale	1.16 ± 0.37	1.46 ± 0.54	0.010
Child-parent separation scale	1.40 ± 0.49	1.80 ± 0.66	0.010
Mask acceptance scale	1.63 ± 0.61	1.96 ± 0.76	0.060

The primary outcome measures demonstrated superior premedication effects with intranasal dexmedetomidine compared to midazolam. The mean Alertness/Sedation scale score was significantly lower (indicating better sedation) in Group D (2.80 ± 1.03) than in Group M (3.70 ± 0.83; p = 0.000). Similarly, anxiety scores were significantly lower in Group D (1.16 ± 0.37) versus Group M (1.46 ± 0.54; p = 0.010), reflecting reduced preoperative anxiety. Child-parent separation scores were also significantly better (lower) in Group D (1.40 ± 0.49) compared to Group M (1.80 ± 0.66; p = 0.010), indicating easier separation from parents. Mask acceptance scores showed a trend toward better acceptance in Group D (1.63 ± 0.61) than in Group M (1.96 ± 0.76), though the difference did not reach statistical significance (p = 0.060). Overall, dexmedetomidine provided more effective sedation, anxiolysis, and facilitation of parental separation, with comparable (non-significant) mask acceptance (Table-2).

Table 3: Distribution of Primary Outcome Scores (%)

Scale / Score	Group D	Group M	p-value
Sedation			0.007
Score 1	6.7	0	
Score 2	43.3	10	
Score 3	13.3	23.3	
Score 4	36.7	53.3	
Score 5	0	13.3	
Anxiety			0.012
Score 1	83.3	53.3	
Score 2	16.7	46.7	
Score 3	0	0	
Separation			0.032
Score 1	60	33.3	
Score 2	40	53.3	
Score 3	0	13.3	
Mask			0.107
Score 1	43.3	30	
Score 2	50	43.3	
Score 3	6.7	26.7	

The distribution of primary outcome scores further highlighted the superiority of intranasal dexmedetomidine over midazolam. For the sedation scale (p = 0.007), a higher proportion of children in Group D achieved deeper sedation levels: 43.3% scored 2 (vs 10% in Group M), while no child in Group D reached score 5 (vs 13.3% in Group M), and fewer remained lightly sedated or awake (score 1: 6.7% vs 0%). Anxiety scores (p = 0.012) showed markedly better anxiolysis in Group D, with 83.3% achieving the lowest anxiety score of 1 (vs 53.3% in Group M) and only 16.7% scoring 2 (vs 46.7% in Group M); no child in either group had a score of 3. Child-parent separation was also significantly easier in Group D (p = 0.032), with 60% scoring 1 (vs 33.3% in Group M) and none scoring 3 (vs 13.3% in Group M). Mask acceptance scores (p = 0.107) showed a non-significant trend favouring Group D, with a higher percentage achieving excellent acceptance (score 1: 43.3% vs 30%) and fewer showing poor acceptance (score 3: 6.7% vs 26.7%). These categorical distributions confirm that dexmedetomidine provided more consistent and deeper sedation, greater anxiety reduction, and smoother parental separation compared to midazolam, while mask acceptance remained comparably acceptable in both groups.

Hemodynamic Parameters Over Time

In our study, MAP was comparable at 0 and 15 min but significantly lower in Group D at 30 min (69.80 ± 7.37 vs 73.80 ± 5.63 mmHg, p=0.02), 45 min (70.46 ± 6.15 vs 75.84 ± 5.51mmHg, p=0.001), and 60 min (73.44 ± 5.54 vs 78.75 ± 5.75 mmHg, p=0.001) (Fig. 1).

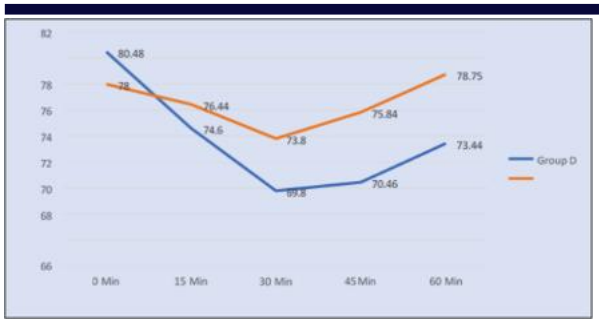

Fig 1: Line Diagram Showing the Mean Pre-operative MAP of Patients in the Two Groups.

In our study, the respiratory rate was comparable at 0 and 15 min but significantly lower in Group D at 30 min (14.73 ± 1.55 vs 15.73 ± 1.43 /min, p=0.01), 45 min (15.16 ± 1.44 vs 16.26 ± 1.55 /min, p=0.006), and 60 min (15.76 ± 1.33 vs 16.86 ± 1.13 /min, p=0.001).

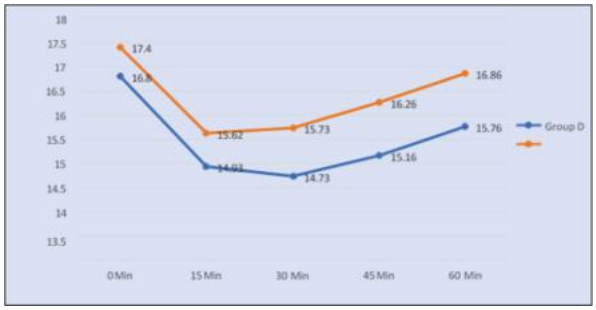

Fig 2: Line Diagram Showing the mean Pre-operative Respiratory Rate of Patients in the Two Groups

The SpO_2 was comparable except at 15 min (96.90 ± 0.54 vs 97.63 ± 0.76 %, p=0.000); all other time points p > 0.05. No episodes of hypotension (SBP drop >20% baseline or age-specific threshold), bradycardia (HR <50 bpm or >30% drop), respiratory depression (SpO_2<90% or RR <10/min), nausea, vomiting or other adverse effects occurred in either group.

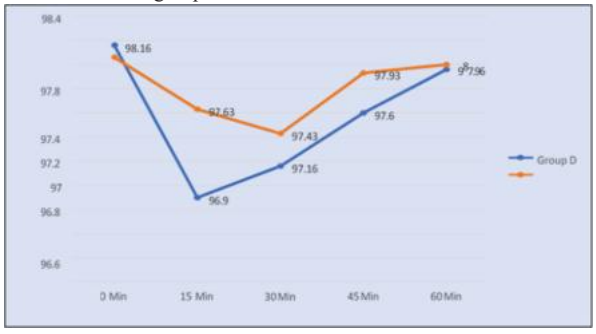

Fig 3: Line Diagram Showing the Mean Pre-operative SpO2 of Patients in the Two Groups.

DISCUSSION

This randomized study demonstrated that intranasal dexmedetomidine (1 µg/kg) provided significantly superior premedication effects compared to intranasal midazolam (0.2 mg/kg) in children aged 2–12 years. Mean scores for sedation (2.80 ± 1.03 vs 3.70 ± 0.83, p=0.000), anxiety (1.16 ± 0.37 vs 1.46 ± 0.54, p=0.010), and child-parent separation (1.40 ± 0.49 vs 1.80 ± 0.66, p=0.010) were lower (better) in the dexmedetomidine group, with categorical distributions confirming more consistent deeper sedation, greater anxiolysis, and easier separation (p=0.007, 0.012, 0.032) (7,8,10). Mask acceptance trended better but was not statistically significant (p=0.060; 0.107 for distribution), aligning with meta-analyses showing comparable induction conditions between intranasal dexmedetomidine and midazolam (7,12).

Baseline comparability ensured unbiased results. Dexmedetomidine caused modest reductions in HR, SBP, DBP, and MAP at later intervals, remaining clinically insignificant without hypotension or bradycardia, consistent with its hemodynamic profile (5,11). Respiratory rate was slightly lower, but SpO_2 stability and the absence of depression or other adverse events (nausea, vomiting) support dexmedetomidine's safety, particularly compared with midazolam in reducing respiratory adverse events (9).

These findings reinforce dexmedetomidine's benefits: sleep-like sedation, no paradoxical agitation, and lower emergence delirium risk (6,12). Limitations include single-center design, subjective scales, and lack of long-term behavioural follow-up. Future multicenter studies could optimize dosing or explore combinations.

CONCLUSION

The study concluded that Intranasal dexmedetomidine 1 µg/kg outperforms intranasal midazolam 0.2 mg/kg as premedication in paediatric patients, delivering superior sedation, anxiolysis, and parental separation with hemodynamic stability and no adverse events. It offers a safe, effective alternative, especially for deeper sedation and reduced agitation.

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