Original Article

A Double-Blind Randomised Controlled Trial Comparing Two Low Doses of Intranasal Dexmedetomidine for premedication in paediatric Day-Care Ophthalmic Patients

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Abstract

Background

Preoperative anxiety in children can complicate anaesthesia induction. Dexmedetomidine, an α2-agonist, provides sedation and anxiolysis without respiratory depression. Its intranasal route offers a non-invasive option ideal for paediatric premedication. However, optimal dosing in ophthalmic day-care settings remains unclear. This study aimed to achieve a calm, cooperative child before induction using a minimally invasive technique with minimal side effects and faster recovery. Two low intranasal dexmedetomidine doses were compared for sedation level, anxiety reduction, induction ease, and safety.

Methods

In this prospective, double-blind, randomised controlled trial, 60 children (3–12 years, ASA I–II) undergoing ophthalmic surgery received intranasal dexmedetomidine 0.5 µg/kg (Group A) or 0.75 µg/kg (Group B). Sedation was assessed at 15 and 30 minutes; hemodynamic parameters were recorded every 10 minutes. Primary outcomes included sedation level, venepuncture distress (after EMLA application), parental separation, and mask acceptance. Secondary outcomes were hemodynamic changes and adverse events.

Results

The 0.75 µg/kg group showed significantly higher sedation at 30 minutes (96.6% vs. 43.3%, $p < 0.001$). Venepuncture tolerance improved markedly, with 80% of children in Group B remaining calm compared to 80% distressed in Group A ($p < 0.001$). Parental separation and mask acceptance were also significantly better in Group B (53.3% satisfactory separation and 70% good mask acceptance; both $p < 0.001$). No significant adverse hemodynamic effects were noted.

Conclusion

Intranasal dexmedetomidine 0.75 µg/kg provides superior sedation, smoother induction, and better cooperation without significant side effects, making it suitable premedication dose for children.

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Article History
Received: 2nd September 2025
Revision: 16th September 2025
Accepted: 20th November 2025
Published: 30th December

How to cite this article: Deepa R S, Suman S R. A Double-Blind Randomised Controlled Trial Comparing Two Low Doses of Intranasal Dexmedetomidine for premedication in paediatric Day-Care Ophthalmic Patients. Ind J Ophthal Anaesth 2025;6(1):2-11

Key words

Intranasal dexmedetomidine, paediatric, premedication, ophthalmic, sedation

Introduction

Preoperative anxiety in paediatric patients is a major concern, often leading to distress and physiological alterations. As a result, there may be increase in secretions, raise in IOP, increase in anaesthetic requirements that may complicate induction, post-operative drowsiness and delirium. Children undergoing ophthalmic surgical procedures are especially susceptible to anxiety, which may be worsened by their inability to open one or both eyes.[1] Anxiety further increases when they are separated from their parents during anaesthesia induction or when they are taken to the preoperative area.[2] Providing anaesthesia to children can be challenging due to the psychological trauma and anxiety caused by maternal separation.[2] This is further compounded by the fact that the preoperative period is the most stressful time for children, with 60% experiencing high anxiety that may persist for up to six months after surgery.[3,4]To overcome this, anaesthetic medications and dose should be designed to relieve children's psychological trauma and anxiety as well as facilitate anaesthesia induction without prolonging recovery. They should also have the properties of being acceptable, having a non-traumatic route of administration to reduce stress to the child, and facilitating the anaesthesia induction process.[2] To achieve the best results, several drugs have been evaluated alongside their route of administration.

Dexmedetomidine (DEX) is one such drug that has good sedative, analgesic, anxiolytic and anaesthetic sparing effects. The sedative properties of dexmedetomidine are largely due to effects on the locus ceruleus, producing a level of consciousness mimicking natural sleep. The mechanism of action of dexmedetomidine works by activating alpha-2 adrenergic receptors in the brain and spinal cord, leading to sedation, analgesia, and sympatholytic effects. This action reduces the release of norepinephrine, a neurotransmitter involved in the stress response, and can also affect pain pathways. The medication helps reduce anxiety and is useful for preoperative anxiolysis and anaesthesia supplementation. Dexmedetomidine can be given either by intravenous or intranasal pathways. However, intranasal (IN) administration of dexmedetomidine is advantageous, as it is non-invasive, avoids first pass metabolism and rapidly enters the bloodstream, leading to rapid sedation. Reports have suggested that intranasally administered dexmedetomidine has a short half-life and a bioavailability of 72.6–92.1%.[5,6,7] Clinical trials using intranasal dexmedetomidine at a dose of 1 μg/kg have produced satisfactory sedation.[8] In some reports, dexmedetomidine intranasally is being used at a higher dose[8,9] and is increasingly used as a paediatric premedication due to its sedative and anxiolytic properties.[10,11] In addition to providing sedation without respiratory depression and reducing emergence delirium, it has also been used postoperatively to reduce aggressive behaviour.[2]

However, optimal dosing strategies for paediatric ophthalmic day-care surgeries remain under debate.

In the present study, we compare the sedative effect, anxiety level and safety profile of intranasal dexmedetomidine at two optimised lower doses of 0.5µg/kg and 0.75µg/kg administered as premedication in paediatric ophthalmic surgical patients. Our study aims to have a quiet and comfortable child on the operating table before induction of anaesthesia using a minimally invasive premedication technique with minimal/no side effects and faster recovery.

Methods

This double-blind, randomised controlled trial was conducted at our super speciality ophthalmic institute. The study adhered to the ethical principles of the Declaration of Helsinki and complied with ICH-GCP guidelines. Ethical approval was obtained from the Institutional Ethics Committee (IEC/2023/19), and the trial was prospectively registered with the Clinical Trials Registry–India (CTRI/2023/08/056530).

Children aged three to twelve years scheduled for elective ophthalmic surgery under general anaesthesia between August 2023 and August 2024 were screened. Only ASA I–II children were included. Exclusion criteria included a known allergy to dexmedetomidine, nasal deformity or trauma affecting intranasal delivery, anticipated difficult airway, obesity, renal/hepatic dysfunction, cardiovascular disease (including bradycardia), respiratory illness, active infection, drowsiness on the day of surgery, or refusal of consent. Written informed consent was obtained from all parents or legal guardians. A total of sixty children met the inclusion criteria and were randomly assigned via computer-generated sequence (www.randomization.com). Group A (n = 30) received intranasal dexmedetomidine 0.5 µg/kg and Group B (n = 30) received 0.75 µg/kg.

On the day of surgery, children arrived at the preoperative area 30 minutes before induction. EMLA cream was applied to the intended cannulation site. Baseline parameters-heart rate, non-invasive blood pressure, respiratory rate, and oxygen saturation-were recorded. Children were positioned in a 30-degree recumbent posture or allowed to lie on a parent's lap. The study drug was administered intranasally in undiluted form by an independent technician to maintain blinding. Dexmedetomidine Hydrochloride (Dexem™, Themis Medicare, India; 100 µg/ml) was delivered using a MAD Nasal mucosal atomisation device. Any immediate reactions, such as coughing, were documented.

Sedation was assessed at 15 and 30 minutes following drug administration using the Ramsay Sedation Score (RSS, scoring 1-6). Hemodynamic parameters, including heart rate, blood pressure, and oxygen saturation, were monitored and recorded at 10-minute intervals throughout the preoperative period. After 30 minutes, intravenous cannulation was performed at the site where EMLA had been applied.The child's behavioural response to cannulation

was assessed using the Groningen Distress Rating Scale (1 = calm, 2 = mild distress, 3 = severe distress but controlled, 4 = severe distress and uncontrolled, 5 = panic). Parental separation was attempted during transfer to the operating room and assessed using the Parental Separation Anxiety Scale (1 = calm/cooperative, 2 = mild fear settling with reassurance, 3 = moderate fear not settling, 4 = crying requiring restraint). If a child became excessively distressed or refused separation, parents were allowed to accompany the child into the induction room to maintain emotional stability and ensure safety. Mask acceptance during induction was assessed using the Mask Acceptance Score (1 = good, accepts mask without resistance; 2 = average, mild resistance easily overcome; 3 = poor, significant resistance requiring additional help). Any adverse effects related to the study drug—such as bradycardia, hypotension, desaturation, nausea, or excessive sedation—were observed and documented.

Sampling

Based on the sample size estimation derived from the study by Diwan et al.[14], and assuming an alpha error of <0.05, a beta error of <0.2 (corresponding to a study power of 80%), the required sample size was calculated. After accounting for an anticipated dropout rate of 10–15%, a total of 60 children were included in the study.

Statistical Methods

Data were analysed using SPSS for Windows, Version 29.0.0 (IBM Corp., Armonk, NY), and Python Version 13.4 for chart generation.

Normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests, and the Central Limit Theorem was considered due to adequate sample size. Categorical variables were summarized using frequencies and percentages, while continuous variables were described using mean and standard deviation or median and interquartile range, based on data distribution. Between-group comparisons for continuous variables were performed using the independent sample t-test or the Mann–Whitney U test. Chi-square test or Fisher's exact test was used for categorical variables. A p-value < 0.05 was considered statistically significant.

Results

A total of 74 children were screened; 8 did not meet the inclusion criteria, and 6 declined to participate. The remaining 60 eligible children were enrolled and randomly assigned to Group A (0.5 µg/kg; n = 30) or Group B (0.75 µg/kg; n = 30)(Figure1).

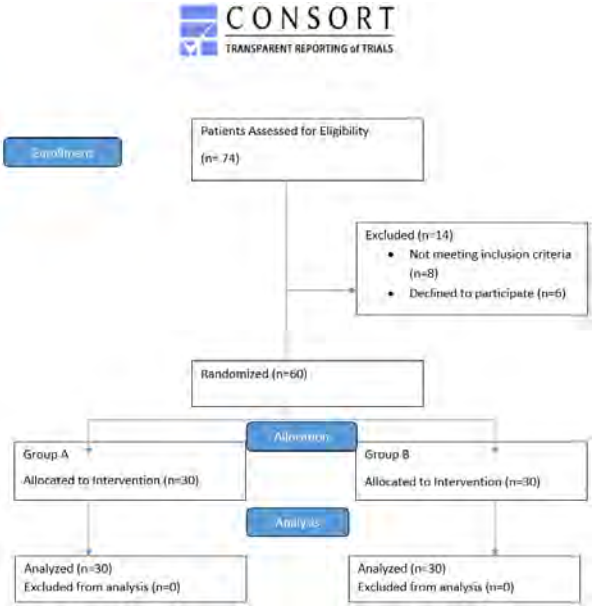


Figure 1: CONSORT flow diagram illustrating the recruitment and progression of participants through the trial.

The demographic characteristics of the two groups, including age, gender distribution and weight, were comparable, with no statistically significant differences between them(Table 1).

Table 1: Demographic distribution in the two groups

	Group A, n=30 (%)	Group B, n=30 (%)	p value
Age in Years (Mean ± SD)	6.17 ± 3.13 Range: 3 - 12	7.33 ± 3.06 Range: 3 - 12	0.149
Gender Male/Female	18 (60%)/12 (40%)	13 (43%)/ 17 (57%)	0.196
Weight in kgs (Mean ± SD)	20.39 ± 7.74 Range: 10.70 - 40.00	25.10 ± 11.81 Range: 14.0-49.0	0.074

At baseline, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation were comparable between the groups. No significant differences were observed at 10 minutes after intranasal administration. By 20 and 30 minutes, children receiving 0.75 µg/kg showed a significantly greater reduction in heart rate and systolic blood pressure than those receiving 0.5 µg/kg (p = 0.003 and p = 0.021)(Figure2 and 3), though values remained clinically acceptable. Diastolic pressure and oxygen saturation did not differ significantly, and intra-operative hemodynamics remained stable in both groups(Figure 4).

Figure 2

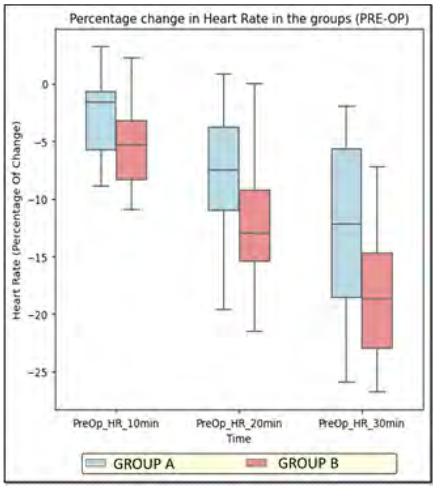


Figure 3

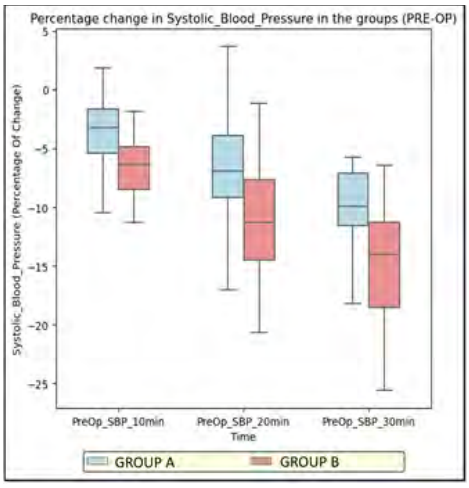
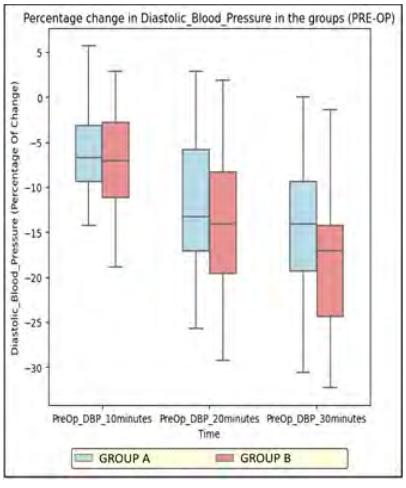


Figure 4



A systolic blood pressure drop >20% occurred only in Group B (7 children; 23.3%), with none in Group A (p = 0.005). No child in either group experienced a ≥30% reduction. Diastolic blood pressure drops >20% or >30% occurred in both groups but were not statistically significant(Table2).

Table 2: Baseline Parameters, Hemodynamic Changes, and Sedation Scores over 30minutes

Parameter	Group A	Group B	p-value
Baseline (0 min)			
HR, Mean ± SD	126.77 ± 16.91 (91–154)	123.17 ± 22.77 (82–154)	0.490
SBP, Mean ± SD	113.67 ± 12.06 (90–134)	117.60 ± 10.99 (86–134)	0.192
DBP, Mean ± SD	67.97 ± 8.64 (50–87)	68.77 ± 6.40 (52–82)	0.746
RR, Mean ± SD	25.97 ± 4.65 (12–36)	23.50 ± 3.55 (18–32)	0.066
SpO_2, Median (IQR)	100 (100–100)	100 (100–100)	0.303
Hemodynamic Changes Over 30 min			
[illegible]	12.59 ± 8.02	17.76 ± 6.86	**0.003**
Time to HR Nadir (min), Median (IQR)	30 (27.5–30)	30 (30–30)	0.175
Max % ↓ SBP (Mean ± SD)	9.94 ± 4.33	14.07 ± 4.53	**<0.001**
Time to SBP Nadir (min)	30 (30–30)	30 (30–30)	0.421
Max % ↓ DBP (Mean ± SD)	15.09 ± 5.53	17.82 ± 7.16	0.166
Time to DBP Nadir (min)	30 (20–30)	30 (30–30)	0.211
BP Decline Thresholds			
SBP ↓ >20%, n (%)	0 (0%)	7 (23.3%)	**0.005**
SBP ↓ >30%, n (%)	0	0	—
DBP ↓ >20%, n (%)	5 (16.7%)	11 (36.7%)	0.080
DBP ↓ >30%, n (%)	1 (3.3%)	3 (10.0%)	0.301
Sedation Scores (RSS)			
RSS at 15 min	1.67 ± 0.55	2.00 ± 0.26	**0.004**
RSS at 30 min	2.43 ± 0.50	3.63 ± 0.67	**<0.001**

Assessment of sedation showed significantly higher Ramsay Sedation Scores in Group B at both 15 minutes ($p = 0.004$) and 30 minutes ($p < 0.001$), indicating more effective sedation with the higher dose. Behavioural responses also favoured Group B, with significantly lower venepuncture distress ($p < 0.001$) and markedly better parental separation and mask acceptance scores ($p < 0.001$), reflecting smoother induction and improved cooperation. No major adverse effects—including bradycardia, significant hypotension, desaturation, vomiting, or excessive sedation—were observed in either group, and all children experienced uneventful and comparable postoperative recovery(Table3).

Table 3: Behavioural Scores: Venepuncture Distress, Parental Separation, and Mask Acceptance

Score Category	Group A, n=30 (%)	Group B, n=30 (%)	P-value
Venepuncture Distress (Groningen Scale)			
Score 1	3 (10.0%)	24 (80.0%)	
Score 2	12 (40.0%)	6 (20.0%)	
Score 3	13 (43.3%)	0 (0%)	
Score 4	2 (6.7%)	0 (0%)	**<0.001**
Parental Separation Anxiety Score			
Score 1	2 (6.7%)	16 (53.3%)	
Score 2	16 (53.3%)	13 (43.3%)	
Score 3	12 (40.0%)	1 (3.3%)	**<0.001**
Mask Acceptance Score			
Score 1	4 (13.3%)	21 (70.0%)	
Score 2	23 (76.7%)	9 (30.0%)	
Score 3	3 (10.0%)	0 (0%)	**<0.001**

Discussion

This study adds to the growing evidence supporting intranasal dexmedetomidine as an effective, minimally invasive premedication in paediatric anaesthesia. The 0.75 μg/kg dose produced superior sedation compared with 0.5 μg/kg, resulting in better cooperation, improved venepuncture tolerance, smoother parental separation, and enhanced mask acceptance. These factors are essential for ensuring a calm, smooth induction and improving the overall perioperative care.

Preoperative anxiety plays a significant role in emergence delirium and postoperative maladaptive behaviours. Kain et al. showed that effective preoperative anxiolysis can improve postoperative behaviour and cognition, emphasising the need for reliable premedication.[15] Several studies support the efficacy and safety of intranasal dexmedetomidine in children. Singla et al. reported sedation comparable to midazolam with stable hemodynamics,[1] while Jun et al. found more satisfactory parental separation with intranasal dexmedetomidine than with other agents.[16] Pharmacokinetic data also support our timing protocol: Yuen et al.[17] reported a median onset of 25 minutes[17] and Wolfe et al. confirmed superior bioavailability with atomised delivery.[18]

Dose-response findings further illustrate how dosing influences sedation quality and safety. Pavithra et al. observed better parental separation with 2 μg/kg than 1 μg/kg, though some children experienced clinically significant hypotension.[19] Ghali et al. similarly reported faster onset with 2 μg/kg delivered via atomiser.[20] However, higher doses increase the risk of bradycardia, hypotension, prolonged sedation, and rare severe complications.[21]

Therefore, our study aimed to identify a dose suitable for day-care practice—one that provides adequate sedation for cannulation under EMLA and calm parental separation while preserving rapid recovery and hemodynamic stability.

Comparable studies support our results. Yuen et al. found 0.5 μg/kg less effective, whereas 1 μg/kg improved sedation at parental separation, consistent with our observation that a slightly higher dose yields better anxiolysis.[7] Ghali et al. also showed that 1 μg/kg provided superior sedation and parental separation compared with midazolam[20]. Yuen et al. later reported that both 1 and 2 μg/kg produced satisfactory sedation in young children, with 2 μg/kg more effective in older children without additional hemodynamic compromise.[8]

Hu et al. reported that although 0.5 μg/kg reduced anxiety, it was inadequate at key stress points and increased postoperative agitation.[22] Higher doses reduced emergence agitation but prolonged PACU stay, highlighting the need to balance sedation with recovery—especially in ambulatory settings. Behrle et al. also observed longer sedation and recovery times with intranasal dexmedetomidine, relevant for high-volume or day care institutes.[13]

Long-term neurodevelopmental safety remains under study, but current evidence is reassuring. Huang et al.[23] showed favourable neurodevelopmental outcomes in infants receiving dexmedetomidine during cardiac surgery[23] and Han et al. reported preserved postoperative cognitive function after tonsillectomy.[24] These findings support the absence of significant neurocognitive harm with dexmedetomidine in paediatric use.

Overall, this study identifies 0.75 μg/kg as an effective and safe intranasal premedication dose for paediatric ophthalmic day-care surgery. It provides reliable sedation, smoother peri-induction behaviour, and stable hemodynamics. Further multicentre trials are needed to establish standardized dosing and to evaluate long-term neurodevelopmental outcomes. Future research should refine dosing strategies to maximise efficacy while ensuring safety.

Conclusion

Intranasal dexmedetomidine at a dose of 0.75 μg/kg provides superior sedation and procedural compliance with minimal side effects in paediatric day-care ophthalmic patients. This dose may be considered optimal for premedication in this population.

Conflict of interest

Nil

Acknowledgement

Dr Sudha, Dr Anup, Dr Ramakrishna, Dr Murali, Dr Swarnagowri for their timely input and constant support

Funding

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