Original Article

Median effective dose of intranasal dexmedetomidine for satisfactory mask induction in children undergoing examination under anaesthesia for retinoblastoma - A prospective up and down sequential allocation study

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ABSTRACT

Background and Aims: Inhalational technique is used to induce anaesthesia in children without intravenous access. We aimed to determine the median effective dose (ED50) of intranasal dexmedetomidine to ensure satisfactory mask acceptance during inhalation induction in children with retinoblastoma undergoing examination under anaesthesia. **Methods:** A prospective sequential allocation study was conducted in children aged 1–60 months divided into Group A (1–18 months) and Group B (18–60 months). Children were administered dexmedetomidine intranasally as premedication. Sedation was assessed using the modified Observer Assessment of Alertness and Sedation Scale until induction. Successful mask acceptance was defined as a cooperative or asleep child during inhalational induction. The starting dose of dexmedetomidine was 1 μg/kg. The next dose varied by 0.2 μg/kg depending on the outcome of this case. According to the Dixon up-and-down method, the mean of midpoints of the failure–success sequence was calculated to obtain the ED50 values. **Results:** The ED50 of intranasal dexmedetomidine for satisfactory mask acceptance was 0.7 μg/kg (95% confidence interval [CI]: 0.54–0.86) in Group A (n = 23) and 0.96 μg/kg (95% CI: 0.83–1.08) in Group B (n = 25) (P = 0.020). The mean (standard deviation) duration of anaesthesia was 33.5 (14.9) minutes in group A versus 23.5 (8.48) minutes in Group B (P = 0.007). **Conclusion:** ED50 was lower in children younger than 18 months than in older children. There was no difference in the time to discharge from the post-anaesthesia care unit despite the procedure being longer in smaller children.

Keywords: Children, dexmedetomidine, facemask, intranasal, inhalation induction, mask acceptance, median effective dose, sedation

INTRODUCTION

Inhalational induction is the usual method for general anaesthesia (GA) in children without intravenous access. A smooth, struggle-free induction provides benefits such as decreased salivation, reduced respiratory complications, a pleasant experience for the child and parent, avoids behavioural disturbance at emergence, and prevents psychological stress and combativeness due to forceful mask holding.[1] Retinoblastoma (Rb) is the most common intraocular malignancy in childhood.[2] Examination under anaesthesia (EUA) is a standard procedure used

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to assess, screen, and diagnose tumour growth or regression in children with Rb to deliver focal therapy and follow-up of children in remission. These children may require around 13–36 EUAs, depending on the stage and severity of the disease.[3] The average age at diagnosis of Rb is 18 months.[2]

Dexmedetomidine is a highly selective α_2 agonist used as a single agent to achieve a sleeping child for painless procedures such as transthoracic echocardiogram and magnetic resonance imaging (MRI). It has been administered through the oral and intranasal routes.[4,5]

This study aimed to find the median effective dose (ED50) of intranasal dexmedetomidine as a premedication to ensure satisfactory mask acceptance during inhalation induction of children with Rb undergoing EUA. The primary outcome was to compare the ED50 of intranasal dexmedetomidine for satisfactory mask acceptance in children aged ≤18 months and those aged >18 months. The secondary objective was to study these doses' haemodynamic stability and recovery characteristics. We hypothesised that younger children would require lower doses of intranasal dexmedetomidine for mask acceptance.

METHODS

This prospective sequential allocation study was conducted between March 2021 and February 2022 at a tertiary care eye centre after obtaining approval from the Institutional Ethics Committee (vide approval number NNEC/C/2021/01/04, dated 28th January 2021) and Clinical Trials Registry-India registration (vide registration number CTRI/2021/02/031258; https://ctri.nic.in/). Details of the anaesthetic technique and study protocol were explained to the parents at the preoperative visit. Written informed consent was obtained from the parents for participation in the study and use of the patient data for research and educational purposes only. The study was conducted in accordance with the ethical principles laid down for medical research by the Declaration of Helsinki, 2013.

The inclusion criteria were American Society of Anesthesiologists (ASA) physical status I–III children aged 1–60 months with Rb undergoing EUA. The exclusion criteria were known allergy to dexmedetomidine, nasal discharge, renal or hepatic dysfunction, and serious systemic diseases. The children were divided into two groups, depending on their age: Group A (>1 month to ≤18 months) and Group B (>18 months to ≤60 months).

All children underwent routine preoperative evaluation for EUA. All children were kept nil by mouth for 6 h for solid food, 4 h for breast milk, and 2 h for clear fluids. A eutectic mixture of lidocaine and prilocaine (EMLA) cream was applied to the dorsum of both hands at least 1 h before the procedure. In the preoperative waiting area, the first child recruited in each group received dexmedetomidine at a dose of 1 μg/kg, dripped into both nostrils by using a 1-mL syringe. The child was kept supine for 1–2 min to ensure absorption. The Modified Observer Assessment of Alertness and Sedation Scale (MOAA/S) score was noted every 10 min after drug administration.[6] The time between drug administration and anaesthesia induction was also recorded. No additional or rescue dose was administered to any child. The case was excluded if the time from drug administration to induction was more than 60 min.

One parent could accompany the child to the operating room (OR) and be present at anaesthesia induction. The anaesthesia was induced on the transport trolley or lap of the parent using gradual, incremental doses of sevoflurane in 100% oxygen (O_2). The heart rate, oxygen saturation, and mask acceptance score, were observed and noted by an independent anaesthesiologist blinded to the dose of intranasal dexmedetomidine used. The mask was held as close to the face as tolerated, and starting from 0% sevoflurane in 6 L/min O_2 through a closed circuit, the dose of sevoflurane was increased by 1% every 3–4 breaths until loss of eyelash reflex. Mask acceptance was scored[7] using a three-point scale (1 = calm, cooperative or asleep; 2 = moderate fear of the mask, cooperative with reassurance; and 3 = combative, crying). A score of 1 or 2 was considered satisfactory. A score of 3 was taken as unsatisfactory mask acceptance. The induction time (start of delivery of the inhalational agent to time to loss of eyelash reflex) was noted. An intravenous (IV) line was secured, and the EUA proceeded. All children were administered IV fentanyl 1 μg/kg, and anaesthesia was maintained using air, O_2, and sevoflurane to maintain an age-appropriate minimum alveolar concentration (MAC) of 1–1.2 according to the patient's need. A suitably sized Ambu® Aura40™ laryngeal mask (Ambu, USA) was inserted when the jaw was relaxed. Spontaneous ventilation was preserved throughout the procedure.

Other details such as the total dose of IV fentanyl received, ophthalmic procedures done (use of focal therapy, including light amplification by stimulated emission of radiation (LASER), cryotherapy, or intravitreal administration of the chemotherapeutic agent), and duration of ophthalmic procedure and anaesthesia were noted. The heart rate and oxygen saturation (SpO_2) were recorded at baseline, induction, 1 min, 5 min, and then at 5-min intervals. Non-invasive blood pressure (NIBP) measurement commenced after anaesthesia induction and continued at 5-min intervals till the end of the procedure. Any untoward events (cough, laryngospasm, secretions, breath-holding, vomiting, bronchospasm, and/or excitement) at induction, maintenance, or recovery were noted. Hypotension or bradycardia was defined as a reduction in blood pressure and heart rate of more than 20% from baseline. At the end of the procedure, the laryngeal mask was removed when the child was awake with purposeful movement, and the child was shifted to recovery. The time to reach a Modified Aldrete recovery score of ≥9 was noted. The endpoint of the study was discharge from the post-anaesthesia care unit (PACU).

For the dexmedetomidine dose (with an initial dose of 1 μg/kg), the subsequent child in each group received intranasal dexmedetomidine with an interval of 0.2 μg/kg, depending on the previous patient's response. If mask acceptance was satisfactory, the dose was decreased by 0.2 μg/kg in the next child. If unsatisfactory, the next child's dose was augmented by 0.2 μg/kg.

The sample size of the two groups was determined according to the Dixon and Massey up-and-down method. Patients were enroled until a minimum of six crossover pairs (from failed mask acceptance to successful mask acceptance) were obtained.[8] Hence, we recruited 23 patients in Group A and 25 in Group B to obtain seven failure-success pairs in each group. Based on a previous study, the starting dose of 1 μg/kg with a step size of 0.2 μg/kg was chosen.[9] The ED50 for intranasal dexmedetomidine for satisfactory mask acceptance was calculated as the average of the crossover midpoints.

The statistical software R environment version. 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to analyse the data. Results on continuous measurements such as age, weight, and time intervals are presented as mean (SD); categorical measurements such as gender, MOAA/S, and mask acceptance scores are presented as numbers. Student's *t*-test was used to find the significance of continuous data, including induction time, duration of procedure and anaesthesia, and recovery time between the two groups. For categorical data, the Chi-square test was used. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics such as age, weight, and gender are mentioned in Table 1. The mean (SD) [95% confidence interval (CI)] time for onset of sleep (MOAA/S score 3) from the time of premedication was 23.7 (9.56) (19.22, 28.17) min in Group A and 27.5 (11.6) (22.43, 32.50) min in Group B ($P = 0.260$). The median MOAA/S score at the time of induction was 2 [interquartile range (IQR): 1–5] (95% CI: 1, 5) in group A and 3 (IQR: 1–4) (95% CI: 2,4) in group B ($P = 0.130$). The median MOAA/S score of children with satisfactory mask acceptance was 1 (IQR: 1-2) was significantly lower compared to those with unsatisfactory mask acceptance of 5 (IQR: 4–6) ($P < 0.001$). The mean (SD) time taken from administration of intranasal dexmedetomidine to induction was 42.5 (21.4) min in Group A and 48.1 (15.9) min in Group B, with the mean difference between the two groups being 5.58 [95% CI: −5.31, 16.47] ($P = 0.310$). The mean (SD) time taken for induction was significantly longer in group B, 116 (35.7) s, compared to group A, 90.8 (29.7) s, with a mean difference of 25.2 [95% CI: 6.03, 44.37] ($P = 0.010$) [Table 2].

The sequences of successful and failed mask acceptance in both groups are shown in Figure 1. The ED50 for successful mask acceptance, as calculated using the Dixon up-and-down sequential allocation method, was 0.7 μg/kg (95% CI: 0.54–0.86) in Group A and 0. 96 μg/kg (95% CI: 0.83–1.08) in Group B ($P = 0.020$).

Nine patients in Group A and four in Group B required additional focal therapy ($P = 0.140$). The number of children with previous anaesthesia exposure was

Table 1: Demographic characteristics

	Group A (*n*=23)	Group B (*n*=25)
Age (months)	11.5 (4.62)	42.2 (13.7)
Weight (kg)	7.73 (1.45)	12.1 (1.53)
Gender (Male/Female)	13/10	12/13

Data is expressed as mean (standard deviation) or numbers. n=number of patients

significantly more in Group B (25/25) compared to Group A (17/23) (P = 0.006). The duration of the procedure and anaesthesia was significantly longer in Group A compared to Group B. There was no significant difference in the length of stay in the PACU between the two groups [Table 2]. Adverse events such as laryngospasm, desaturation, oculocardiac reflex, regurgitation, vomiting, and apnoea were not observed in either group.

DISCUSSION

In this dose-response trial, we observed that the ED50 of intranasal dexmedetomidine was lower in younger children (0.7 μg/kg) than in children aged 18–60 months (0.96 μg/kg).

Other authors have also concluded similarly that infants need lower doses than toddlers.[4,10,11] In determining the ED50 of intranasal dexmedetomidine after failed chloral hydrate sedation, it was observed that higher doses were required with advancing age.[12] A pharmacokinetic study observed increased peak concentration levels (Cmax) in younger children. This could be attributed to the larger volume of distribution, relatively lower metabolic enzyme activity, slow drug clearance, and immature blood–brain barrier, as well as the effect of sleep deprivation in smaller children.[13]

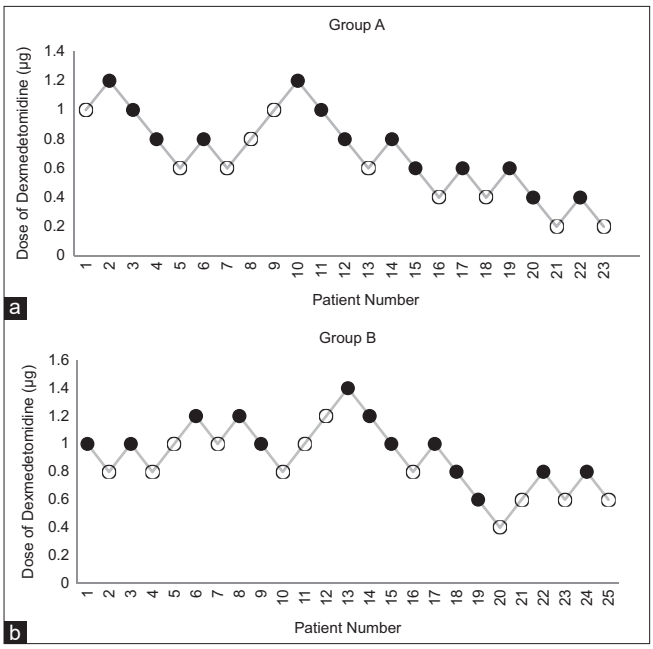

Figure 1: Dexmedetomidine dose (a) children aged <18 months, (b) children aged 18–60 months. Solid circle represents satisfactory mask acceptance. An open circle represents failed mask acceptance

The ED50 of intranasal dexmedetomidine as the only anaesthetic agent for transthoracic echocardiography has been estimated to be around 1.8–3.3 μg/kg.[4,14] When used as the sole sedative for MRI, a retrospective chart review showed a 96% success rate with 4 μg/kg intranasal dexmedetomidine.[5] In one study, 80% of children receiving 1 μg/kg intranasal dexmedetomidine showed satisfactory behaviour at induction, although one-third woke up during transfer from the preoperative area. They also observed that 0.5 μg/kg dose induced sleep, but children were readily awakened and distressed at induction.[9] Even in our study, three children in Group A and five in Group B were awake at induction but could be persuaded to accept a mask. The dose of intranasal dexmedetomidine for paediatric sedation varies with age, procedure, and other child-related factors. The dose required for premedication to ensure calm induction is lower than that needed for a single anaesthetic agent for painless procedures requiring immobility (echocardiography, MRI, evoked potential recording, etc.). In the former case, the role of dexmedetomidine is to facilitate mask acceptance while the child drifts from sleep to anaesthesia, whereas in the latter, its function is to ensure immobility despite external stimuli such as touch or noise throughout the procedure.[13]

Compared with midazolam, dexmedetomidine is a superior sedative but a poorer anxiolytic.[7] Its adjuvant analgesic effect may prove advantageous in Rb children, especially those who receive focal therapy during the EUA. The time between intranasal dexmedetomidine administration and induction in our study is consistent with other reports in the literature.[7,13,15] Uusalo *et al*.[13] calculated the median

Table 2: Characteristics of sedation, induction, recovery times and duration of procedure

	Group A (n=23)	Group B (n=25)	Mean difference (95% CI)	P
Time between drug administration and induction (min)	42.52 (21.4)	48.1 (15.9)	5.58 (−5.31, 16.47)	0.310
Induction time (s)	90.8 (29.7)	116 (35.7)	25.2 (6.03, 44.37)	0.011
Duration of procedure (min)	22.6 (12.13)	14.7 (5.8)	7.9 (2.45, 13.35)	0.005
Duration of anaesthesia (min)	32.8 (14.8)	23.2 (8.48)	9.6 (2.66, 16.53)	0.007
Time to discharge from post anaesthesia care unit (min)	34.4 (18.3)	27.3 (19.3)	7.1 (−3.85, 18.05)	0.200

Data is expressed as Mean (standard deviation), CI: confidence interval of difference of means

time to maximal effect after intranasal dosing to be 45 min. They, however, opined that additional agents may be required in combination with intranasal dexmedetomidine for procedural sedation.

The duration of the EUA was significantly higher in Group A as these children had active tumours requiring more extensive evaluation and focal therapy such as laser or intravitreal injection than those in group B, many of whom were in the follow-up phase. Nevertheless, the time to discharge from the PACU was similar in both groups and comparable with other reports in the literature.

Intranasal dexmedetomidine, at doses used in our study, has not been found to cause clinically significant haemodynamic or respiratory compromise requiring intervention.[7,12,14]

We did not study separation anxiety as the parent accompanied the child to the OR. This practice avoided arousal by external stimulation during the transfer from the preoperative area to the OR. Our results would have been more precise if we had controlled for the sleep status between dexmedetomidine administration and at induction as it appears that satisfactory mask acceptance after intranasal dexmedetomidine is due to its sedating effect.[7] The lack of adverse effects may need to be validated in a larger sample size. A larger study group may also facilitate the estimation of ED95 using other statistical methods such as probit regression and help to compare children receiving repeat sedation with those receiving first-time sedation.

CONCLUSION

The ED50 of intranasal dexmedetomidine for satisfactory mask acceptance in children aged 1–18 months (0.7 μg/kg) is significantly lower than ED50 for the age group of 18–60 months (0.96 μg/kg). There was no difference in the time to discharge from PACU despite the procedure being longer in smaller children.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

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Conflicts of interest

There are no conflicts of interest.

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