Original Article

Intranasal atomized dexmedetomidine versus intranasal atomized midazolam in preventing emergence delirium in children undergoing ocular surgery with sevoflurane anaesthesia: a randomized blinded trial.

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Abstract

Background

Midazolam and dexmedetomidine have been shown to reduce the incidence of emergence delirium (ED) in children undergoing surgery. Literature comparing the effectiveness of dexmedetomidine versus midazolam, when both drugs are administered via atomization intranasally, in reducing ED in paediatric ocular surgery is lacking. Our study was conducted to explore this lacuna in clinical literature.

Design and Methods

Prospective, double-blinded and randomized. A total of 98 children scheduled to undergo elective ocular surgery were randomized to receive either 2 mcg/kg dexmedetomidine or 0.2 mg/kg midazolam, intranasally via atomization. General anaesthesia was induced and maintained with sevoflurane. The incidence of ED, preoperative sedation, preoperative anxiety and parental satisfaction were measured.

Results

A total of 19 (39%) children in the midazolam group had ED, compared to 5 (10%) in the dexmedetomidine group (relative risk 0.26, 95% CI: 0.11-0.65; p=0.004). The median (IQR) Paediatric Anaesthesia Emergence Delirium scores were lower in the dexmedetomidine group, compared to the

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midazolam group on arrival in the PACU, 10, 20, 30 and 40 minutes in the PACU ($p<0.05$). Children in the dexmedetomidine group were more sedated and less anxious following premedication, compared to the midazolam group ($p<0.05$).

Conclusion

Preoperative intranasal atomized dexmedetomidine is more effective in reducing the incidence of ED in children undergoing ocular surgery, compared to intranasal atomized midazolam.

Keywords

Emergence delirium; ocular surgery; midazolam, dexmedetomidine, intranasal, atomization

Introduction

Ophthalmic surgeries represent a high-risk group of surgeries for emergence delirium (ED) in paediatric patients.[1] Failure to prevent, or timely treat ED, in the postoperative period may lead to negative consequences like dislodgment of the intravenous cannula, unintended patient injury and delay in discharge from the post-anaesthesia care unit (PACU). ED can also cause increase in the intraocular pressure and the child inadvertently disturbing the surgical dressing, leading to potential surgical complications following ocular surgery.[2]

Several pharmacological options have been used to prevent and incidence of ED in children undergoing surgery.[2] Midazolam has been extensively studied for its role in reducing preoperative anxiety, parental separation and postoperative ED in paediatric surgical patients.[3] While midazolam is effective in reducing preoperative anxiety, its role in reducing ED is, rather, uncertain.[4] Moreover, midazolam has been known to cause paradoxically excitation in some patients, and the risk-factors and pathophysiology for this phenomenon is poorly understood.[5] Dexmedetomidine, a centrally acting selective alpha-2 receptor agonist, has anxiolytic and sedative properties, and has been shown to be a safe and effective premedicant in children.[6]

The low (and often unpredictable and variable) bioavailability of oral midazolam and dexmedetomidine resulted in exploration and clinical evaluation of the intranasal route for administration of these drugs preoperatively.[7,8] However, administering drugs as nasal drops in children could result in coughing, sneezing and poor patient acceptance, besides most of the drug running off the back of the throat and either swallowed or spat out, either way resulting in low systemic bioavailability.[9] More recently, alternate drug delivery systems like mucosal atomizer devices (MADs) have been developed to improve the effectiveness of intranasal drug administration. MADs deliver drugs as a fine spray over a larger nasal mucosal surface area, and hence could be more effective to the traditional droplet technique of intranasal drug instillation[10]. Literature regarding the effects of atomized dexmedetomidine versus atomized midazolam on the incidence of ED in paediatric patients is currently lacking.

This study was, hence, conducted to evaluate the effect of dexmedetomidine versus midazolam, with both drugs atomized intranasally via a MAD,on the incidence

of ED in paediatric patients undergoing elective ocular surgery under sevoflurane anaesthesia. We hypothesized that intranasal atomized dexmedetomidine would be more effective than intranasal atomized midazolam in preventing ED in these patients. The effect of these drugs on preoperative anxiety, preoperative sedation, inhalational anaesthesia induction characteristics and postoperative pain were the secondary outcomes of our study.

Materials and Methods

Study design and participants

This study was a prospective randomized double-blinded trial that was conducted in a university teaching hospital in northern India from April 2020 to October 2020. Prior approval from the university ethics committee was obtained (NK/5646/MD/936 dated 15th October 2019) and the study protocol registered prospectively with the National Clinical Trials Registry (CTRI/2020/03/023752 dated 04/03/2020). As part of the study, 98 ASA I and II children, aged 3-11 years and scheduled to undergo elective ophthalmic surgery under sevoflurane anaesthesia were included. Consent was obtained from the parents/legal guardians at the time of enrollment. Children with known allergy to dexmedetomidine/midazolam, those with developmental delay and those with psychological and/or neurological disorders were excluded from the study.

Patients were consecutively screened for potential enrollment, following which they were randomly allocated into either of two groups. The participants in the 'Midazolam group' received 0.2 mg/kg midazolam (Midaz 5mg/ml, Ahaan Healthcare Pvt Ltd, Satara, MH, India) intranasally via a MAD (MIRAD, Marshall Airway Products, Radstock, UK). The participants in the 'Dexmedetomidine group' received 2 mcg/kg of intranasal dexmedetomidine (Dexem 100 mcg/ml, Themis Medicare Ltd, India) via the MAD mentioned earlier. The study drugs were instilled into both nostrils of the patient, in the recumbent position. The dead space in the atomizer was primed with the drugs prior administration, and the study drug injected rapidly to ensure adequate atomization.

The randomization was performed by computer-generated randomization, with the allocation sequence concealed in consecutively numbered and sealed envelopes. The preparation and administration of the study drugs were overseen by an independent investigator who was not involved in the administration of anesthesia or the assessment of our study's outcomes. The participants, parents, surgeons, attending anaesthesiologist and the independent observers in the preoperative holding area and the PACU were blinded to group allocation.

Perioperative anaesthesia protocol

All the study participants were fasted as per standard institution protocol (6 hours and 1 hour for solids and clear liquids, respectively).Premedication was administered, as determined by group allocation, 30-minutes prior surgery in the

preoperative holding room in the presence of the parent.

Anaesthesia was induced with sevoflurane in 100% oxygen. The airway was secured with an appropriately sized iGEL® supraglottic airway device (Intersurgical Ltd, Berkshire, UK) after obtaining intravenous access and the injection of 2 mcg/kg of fentanyl intravenously. Anaesthesia was maintained with sevoflurane in 50:50 nitrous-oxide: oxygen mixture at a combined MAC of 1.2. The children were monitored for continuous ECG, heart rate, oxygen saturation, and non-invasive blood pressure recorded at 10 minute intervals. Additional intraoperative rescue analgesia consisted of 0.5 mcg/kg of fentanyl to maintain haemodynamics within 20% from baseline. All patients received 15 mg/kg of paracetamol and 0.1 mg/kg of ondansetron intravenously towards the end of the surgical procedure. At the end of surgery, inhalational anaesthetics were stopped and the supraglottic airway device removed in the deep plane of anaesthesia. The child was shifted to the PACU for observation when fully awake.

All the participants were monitored in the PACU for 3 hours, as per standard institutional practice. The children were then discharged from the PACU, either to the ward or home when the child was awake, had no nausea-vomiting and was pain free.

Primary outcome

An independent observer assessed the level of ED in the child using the Pediatric Anesthesia Emergence Delirium (PAED) scale at the time of arrival in the PACU and then at every 10-minute intervals, until 1 hour postoperatively.[11]

Secondary outcomes

i. Preoperative patient sedation following premedication was assessed by a blinded observer using the Modified Observers' Assessment for Alertness/Sedation scale (MOAAS) at baseline and then at 10, 20 and 30 minutes after premedication.[12] For our study purpose, a MOASS score of less than 3 was considered a satisfactory sedation.

ii. Preoperative patient anxiety was measured using the modified Yale Preoperative Anxiety Scale (mYPAS).[13] It is an observational measure of children`s preoperative anxiety consisting of 22 items divided into 5 categories: activity, vocalization, emotional expressivity, state of arousal and use of the parent. The total score ranges from 22.5 to 100, with higher scores indicating higher anxiety levels.

iii. Pain in the postoperative period was assessed using the Face Legs Activity Cry and Consolability (FLACC) scale.14 A FLACC score of > 4 was considered significant and treated with 0.5 mcg/kg of rescue fentanyl, given intravenously.

iv. Parental satisfaction was evaluated using a 5-point Likert score (1 – highly unsatisfied to 5 – highly satisfied), at the time of discharge of the patient from the PACU.

Statistical analysis

The incidence of ED following ocular surgeries is reported at approximately 50%. An earlier study had demonstrated an incidence of ED of 30% with intranasal midazolam premedication.[15] Assuming a 25% reduction in ED incidence with preoperative dexmedetomidine, the total sample size of 96 participants was calculated. We aimed to recruit at least 100 children, to account for drop-outs.

All data collected from the study proforma were presented using measures of central tendency and dispersion. The incidence of ED was analysed using the Chi square test and presented as number (percentage) and relative risk (with 95% confidence intervals). Normality of data was tested using Kolmogrov-Smirnov test of normality. The Student's t-test and Mann-Whitney U test were used to compare normal and skewed distributed data, respectively All tests were performed at an alpha significance of 0.05. SPSS Version 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

Results

A total of 113 children were assessed for study enrollment, of which 100 were randomized. 2 patients (one in each group) were excluded from the final analysis due to violation of the study protocol, resulting in the data of 98 participants being subjected to the final analysis (Figure 1). Both groups were well-matched in terms of their demographic and surgical data, with no statistically significant difference between them (Table 1).

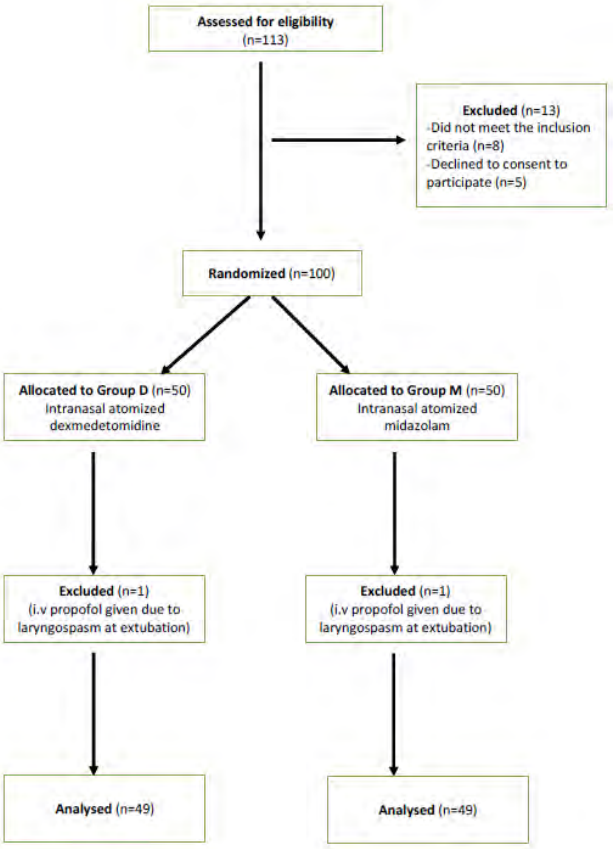

Figure 1 CONSORT Flowchart

Table 1: Demographic and operative data

	Dexmedetomidine group (n=49)	Midazolam group (n = 49)
Age (years)	5.61 ± 2.22	5.96 ± 2.37
Weight (kg)	19.84 ± 4.67	21.33 ± 6.33
Male:Female, n (%)	33:16 (67:33)	29:20 (59:41)
ASA- I n (%)	49 (100)	49 (100)
Parental presence during induction	9 (18)	14 (28)
Duration of anaesthesia (min)	40.59 ± 8.08	39.55 ± 7.26
Duration of surgery (min)	33.88 ± 9.21	35.08 ± 5.07

Data expressed as mean + SD, unless stated otherwise
ASA – American Society of Anesthesiologists

Primary outcome

A total of 19 (39%) children in the midazolam group had ED, compared to 5 (10%) in the dexmedetomidine group (relative risk 0.26, 95% CI: 0.11-0.65; p=0.004). This represents a relative risk reduction (95% CI) of 0.74 (0.35-0.89), and an absolute risk reduction (95% CI) of 0.28 (0.13-0.45) with intranasal atomized dexmedetomidine.

The numbers need to treat (95% CI) was 3.5 (2.24-7.99) for intranasal atomized dexmedetomidine, compared to intranasal atomized midazolam. The children in the dexmedetomidine group took longer to extubate at the end of the surgery, compared to the midazolam group (7.2 + 1.7 min vs 4.6 + 1.7 min, p=0.0001). However, this difference was not clinically significant. The median (IQR) PAED scores were lower in the dexmedetomidine group, compared to the midazolam group and the difference was statistically significant on arrival in the PACU, 10, 20, 30 and 40 minutes in the PACU (Table 2)

Table 2: PAED and FLACC scores at different time points after surgery

	Dexmedetomidine group (n=49)	**Midazolam group (n=49)**	**p-value**
PAED score			
Arrival in PACU	0[0-0]	0[0-2]	**0.0001**
10 min	2[1-2]	4[2-6]	**0.0001**
20 min	4[2-5]	7[5-9]	**0.0001**
30 min	7[5-8]	8[7-10]	**0.001**
40 min	7[5-9]	8[7-10]	**0.002**
60 min	4[3-7]	5[4-7]	0.08
Highest score	9[8-10]	9[9-12]	**0.001**
FLACC score			
Arrival in PACU	0[0-0]	0[0-0]	0.13
10 min	2[1-2]	2[2-3]	0.17
20 min	4[3-5]	5[4-5]	0.11
30 min	3[2-4]	3[3-4]	0.73
40 min	3[2-4]	3[2-3.5]	0.75
60 min	2[1-3]	2[1-3]	0.86
Highest score	5[4-5]	5[4-5]	0.14

All data expressed as Median[IQR}; p < 0.05 is significant
PAED – Paediatric Anaesthesia Emergence Delirium;
FLACC – Face Legs Activity Cry Consolability

Secondary outcomes

Children in the dexmedetomidine group were more sedated preoperatively, as compared to those belonging to the midazolam group. The Median[IQR] MOASS scores were lower in the dexmedetomidine group than the midazolam group at 10,20 and 30 minutes following premedication, and the difference was statistically significant. The baseline preoperative anxiety, measured using the mYPAS score, was comparable between the two groups. However, the mean + SD mYPAS scores were lower in the dexmedetomidine group compared to the midazolam group at 10, 20 and 30 minutes following premedication, and the difference was statistically significant (Table 3). None of the children in the midazolam group had any paradoxical excitation following premedication.

Table 3: Preoperative characteristics

	Dexmedetomidine group (n=49)	**Midazolam group (n=49)**	**p-value**
Pre-operative MOAAS[1]			
Baseline	6[6-6]	6[6-6]	1.0
10 min	5[5-5]	5[5-5]	**0.04**
20 min	3[2-4]	4[4-4]	**0.0001**
30 min	2[1-3]	3[2-4]	**0.0001**
Preoperative mYPAS[2]			
Baseline	75.48 ± 14.87	79.27 ± 15.73	0.22
10 min	53.47 ± 13.66	64.50 ± 9.26	**0.0001**
20 min	49.47 ± 8.59	57.39 ± 9.52	**0.0001**
30 min	41.99 ± 12.83	50.40 ± 14.14	**0.003**

[1]Expressed as Median[IQR]; 2Expressed as Mean + SD; p < 0.05 is significnat
MOAAS – Modified Observer Assessment Alertness/Sedation Score; mYPAS – Modified Yale Preoperative Anxiety Score

The highest median[IQR] postoperative FLACC scores was comparable between the 2 groups (5[4-5] vs5[4-5], p=0.17), as were the median[IQR] FLACC scores at baseline, 10, 20, 30 and 40 minutes postoperatively (Table 2). Although the number of children requiring rescue analgesia in the dexmedetomidine group were lower compared to the midazolam group (6% vs 16%), the difference was not statistically significant (p=0.11).

The children in the dexmedetomidine group had a lower mean + SD heart rate, than those in the midazolam group, at all-time points after premedication, the intraoperative period and in the PACU. However, none of the participants in the dexmedetomidine group had symptomatic bradycardia requiring treatment. All the study participants, regardless of their group allocation were discharged from the PACU at 3 hours postoperatively. The home-discharge and ward admission rates were comparable between the two groups. Parents of the dexmedetomidine group had a higher median[IQR] satisfaction score than those of the midazolam group (4[3-5] vs 3[2-4]), and the difference was statistically significant (p=0.04).

Discussion

We demonstrated that premedication with intranasal atomized dexmedetomidine significantly reduced the incidence of ED, compared to atomized midazolam, in paediatric patients undergoing ophthalmic surgeries under sevoflurane anaesthesia.

Children in the dexmedetomidine group were more sedated preoperatively, as compared to those belonging to the midazolam group. The Median[IQR] MOASS scores were lower in the dexmedetomidine group than the midazolam group at 10,20 and 30 minutes following premedication, and the difference was statistically significant. The baseline preoperative anxiety, measured using the mYPAS score, was comparable between the two groups. However, the mean + SD mYPAS scores were lower in the dexmedetomidine group compared to the midazolam group at 10, 20 and 30 minutes following premedication, and the difference was statistically significant (Table 3). None of the children in the midazolam group had any paradoxical excitation following premedication. The relative risk of ED with intranasal atomized dexmedetomidine was 0.26 (95% CI: 0.11-0.65), representing an absolute risk reduction of 28% compared to atomized midazolam administered intranasally.

Ophthalmological surgery is considered an important risk factor for the development of ED in paediatric patients, and several reasons have been attributed to this phenomenon.[1,2] Preoperative patient anxiety, the use of sevoflurane for induction and maintenance of general anaesthesia for these short-lasting surgeries, visual disturbances caused by the primary disease or the surgical procedure, patching of the operated eye in the immediate postoperative period and the associated lack of visual stimuli, and the child's fear of darkness have all be proposed

as potential reasons for high ED in children undergoing eye surgeries.[16] Thus, it is important to take measures to reduce the incidence of ED in this surgical patient group. In several centers across the world, nursing staff in the preoperative holding area are responsible for the administration of premedication before surgery. Furthermore, nursing staff in the PACU need to be able to identify ED and respond to it appropriately to prevent negative consequences for the pediatric patients and their parents. Thus, knowledge about ED and their involvement in operating room policies to prevent postoperative ED is crucial.

Midazolam and dexmedetomidine have been used as premedication in paediatric surgical patients to reduce ED via the oral and intranasal routes, and the results are inconsistent.[3] Theoretically, the intranasal route administration offers several advantages over the oral route. The absorption of the drug across the vascular nasal mucosa is faster, resulting in a quicker onset. Moreover, by escaping hepatic first-pass metabolism, the systemic bioavailability of intranasally administered midazolam and dexmedetomidine is higher than the oral route. One of the main reasons for low efficacy of intranasal premedication is coughing or sneezing by the child when the drug is being administered. Furthermore, when administered as drops, a considerable fraction of the drug can run off the back of the throat resulting in low systemic bioavailability.[17,18] This could explain the inconsistent results of studies evaluating intranasal midazolam and dexmedetomidine premedication, using the droplet technique of drug administration. The use of MADs has improved safety and ease of intranasal drug administration, and have been increasing used for administering premedication to paediatric surgical patients. Unlike the traditional droplet route, MADs deliver drugs as a fine spray over the vascular nasal mucosa, resulting in negligible (if any) drug run-off and wastage.[19] We have recently used MADs for delivering intranasal premedication in paediatric patients in our ophthalmological operating theatres, and found the technique easy to use, efficacious and acceptable to our patients, the parents and nursing staff.[20]

The incidence of ED in the midazolam group reported in our study, was 39% which was lower than an earlier study by Singla et al[21] from our center on paediatric surgical patients receiving midazolam premedication. Singla et al[21] studied children undergoing a heterogenous group of surgeries that included apart from ophthalmic surgeries, also urogenital and other superficial surgeries. However, while Singla et al[21] used oral midazolam at a dose of 0.3 mg/kg, we used intranasal atomized midazolam at a dose of 0.2 mg/kg, which could be more efficacious. In our study, the incidence of ED in the dexmedetomidine group was lower which is in agreement with other studies evaluating dexmedetomidine premedication for ED.[22] The doses of intranasal midazolam (0.2 mg/kg) and intranasal dexmedetomidine (2 mcg/kg) were chosen based on earlier published studies.[23,24]

Early postoperative pain is another important risk factor for ED, but is unlikely to be a confounding factor in our study. All our patients received 2 mcg/kg intravenous fentanyl for intraoperative and postoperative analgesia, in addition to intravenous paracetamol at the end of surgery. The median FLACC pain scores were relatively low in our study participants, and comparable between the two groups.

The current study has some important strengths. Firstly, our study was performed in a homogenous patient population scheduled to undergo eye surgery, known to be associated with a high incidence of postoperative ED. Secondly, to the best of our knowledge, ours is the first study to compare the effect of intranasal dexmedetomidine with intranasal midazolam for the prevention of ED in paediatric patients, when both the drugs were administered using a MAD. Atomization has been shown to be associated with lesser coughing and spitting, resulting in higher patient acceptability. There were some limitations to our study. We did not measure postoperative sedation in our study participants, which could affect PACU discharge times. However, in our study, none of the study participants failed to be discharged from the PACU at 3 hours postoperatively. Secondly, we did not measure preoperative anxiety in the parents, which could have an influence on the ED rates reported.

Thus, to conclude, preoperative intranasal atomized dexmedetomidine is superior to intranasal atomized midazolam in preventing ED in children undergoing ocular surgeries under sevoflurane anaesthesia. The preoperative use of intranasal atomized dexmedetomidine in this patient group was associated with greater preoperative sedation, lesser preoperative anxiety and greater parental satisfaction. Our study findings would need to be explored in other clinical and surgical settings.

Conflict of interest

None declared

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