Midazolam-Dexmedetomidine Combination versus Midazolam Alone for Premedication in Children Undergoing Pediatric Cataract Surgeries: a Double-Blinded Randomized Controlled Trial

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Background:Dexmedetomidine, a selective α2 agonist has shown promising results when used as a premedicant. This prospective randomized study evaluated the efficacy of two different premedication regimens in achieving a smooth conduct of anesthesia and optimum pain relief in pediatric cataract surgeries. **Methods:**90 ASA I or II children, aged 1-6 years, scheduled for elective cataract surgeries were randomized to receive either 0.25 mg kg-1oral midazolam and 1µg kg-1 of intranasal dexmedetomidine (Group MD; n=45) or 0.5mg/kg oral midazolam followed by 0.02ml kg-1 intranasal saline drops (Group MS; n=45) 45 min prior to surgery. Drug acceptance, anxiety at parental separation and quality of mask induction was evaluated. Subtenon block was given to all the children. Intraoperative use of narcotics was avoided and used only as rescue drug. Primary outcome of the study was number of patients requiring rescue analgesia over 24-hour period. The secondary outcomes were time to first rescue analgesia, frequency of rescue analgesia, incidence of OCR and PONV.**Results**:90% of the children in Group MD achieved MOAA/S ≤ 4 at 30 minutes versus 95% in Group MS. Drug acceptability, parental separation and mask acceptance were similar in both groups. Incidence of PONV and children who required rescue analgesia was less in MD group compared with MS group. There was no event of OCR in both groups. **Conclusion**: Premedication with combined IND and low dose oral midazolam is superior in decreasing postoperative analgesic requirements when compared to routine oral midazolam premedication alone in pediatric cataract surgeries under general anesthesia.

Keywords; Premedication, paediatric, intranasal dexmedetomidine, midazolam, cataract

Introduction

Dexmedetomidine, a α_2 selective agonist with its unique pharmacokinetics is useful for patients susceptible to perioperative stress.[1] Intranasal dexmedetomidine (IND) 1µg kg-1 has been shown to provide an early sedation and good parental separation but with little improvement in mask acceptance.[2] Midazolam with its proven beneficial effects, if combined with unique features of dexmedetomidine may prove to be ideal for premedication. Hence, this study was conducted to assess the effects of combined oral midazolam and IND premedication with oral midazolam alone, in paediatric cataract surgeries.

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Received: 10/03/2021
Accepted: 24/03/2022

DOI: https://doi.org/10.4038/slja.v30i1.8802

Materials and methods

After approval by the institutional ethical committee (8848/PG-2Trg/2011/975), this prospective randomized double-blind study was conducted in the Department of Anaesthesia at a tertiary care hospital. Ninety children, aged 1-6years,belonging to American Society of Anesthesiologists (ASA),physical status I-II were enrolled for the study after written informed consent from parents/ legal guardians. They were explained regarding the usage of Numeric Rating Scale (based on a 0–10mm scale, 0mm= no pain and 10mm=worst pain imagined) to assess the child's postoperative pain.The exclusion criteria were children with recent upper respiratory tract infections,allergy to study drugs,coagulation abnormalities and associated anomalies demanding deviation from standard protocol.

After recommended fasting of 6 hours for solids and 2 hours for clear fluid,children were divided into two groups using computer generated permuted block randomization, in blocks of 10patients in a 1:1 ratio using opaque sealed envelopes. The premedication drugs were prepared by an anesthesiologist not involved in the study. All patients were allocated to receive either low-dose oral midazolam and IND combination or oral midazolam with equivalent amount of intranasal saline.The anaesthesiologist, surgeon and observer all were unaware of the drug.

Children in group MD were premedicated with 0.25mg kg-1 oral midazolam and 1µg kg-1 of dexmedetomidine IV preparation (50µg per 0.5ml) administered intranasally 30-45minutes before the procedure. A 1ml syringe was used for dripping dexmedetomidine equally in both nostrils in recumbent position.Children in group MS were premedicated with 0.5mg kg-1 oral midazolam commercial preparation (2mgml-1)followed by 0.025mg/kg normal saline intranasally 30-45mins before procedure.

Hemodynamic and respiratory parameters were continuously monitored and documented every 10minutes after the administration of study medications. Pre-sedation behavior of the child was assessed using a four-point scale (1=Calm, Co-operative, 2=Anxious but reassurable, 3= Anxious and not reassurable, 4= Crying or resisting).[3] Drug acceptability was recorded as either good/fair/poor. Modified Observer's Assessment of Alertness/Sedation scale [4] (Appendix-1) was used to assess sedation and recorded every 10 minutes. MOAA/S ≤4 was considered as adequate sedation. A four-point Parental Separation Anxiety Scale (PSAS) was used to assess parent child separation (Appendix-2). Scores 1, 2 were taken as 'Satisfactory' and Scores 3, 4 as 'Unsatisfactory' separation from parents.

Standardized anaesthesia induction regimen was followed, with sevoflurane 8% in a 40%:60% mixture of oxygen/nitrous oxide using a face mask. The degree of mask acceptance was assessed using a three point scale (1= Calm, cooperative or asleep, 2= Moderate fear of the mask, cooperative with reassurance, 3=Combative, crying).[3] Scores 1 and 2 were taken as 'Satisfactory' and score 3 as 'Unsatisfactory' mask induction. After induction, intravenous access was established and injection paracetamol 15 mg kg-1 was given. An appropriate size LMA was inserted number of attempts for insertion were noted. Following induction, children were given subtenon block (STB) using 0.08 ml kg-1 of 0.75% ropivacaine. All the blocks were performed by same surgeon.

All the children were continuously monitored for HR, NIBP, SPO_2, $ETCO_2$ and RR after induction (baseline), after insertion of LMA, at STB injection, at start of surgery, and then at 5-minute intervals until the completion of surgery. At the end of surgery, 100% O_2 was administered and LMA removed once child achieved spontaneous and regular breathing. Postoperatively pain scores were assessed using the Faces, Legs, Activity, Cry, Consol ability (FLACC) score.[5]Injection fentanyl 0.5µg kg-1 was given if FLACC score was >3, as first rescue analgesia. Ondansetron 0.1mg kg-1 was

given in case of emesis. All children stayed in postoperative room for at least 3hours as per institution protocol. Parents were asked to administer paracetamol 15mg kg-1 syrup as second rescue analgesia at 6hours interval, if NRS assessment score was >3 at home. All parents were contacted next day on phone and adequacy of analgesia during the first 24hours of postoperative period was judged on a 3point score:0-unsatisfactory,1-noncommittal,2-satisfactory.

The primary outcome of the study was to assess the number of children who require rescue analgesics during the 24hour study period. The secondary outcome measures were time to first rescue analgesia, frequency of rescue analgesic, incidence of OCR(oculocardiac reflex), pain scores and PONV(Postoperative nausea vomiting).OCR was defined as an abrupt decrease in heart rate by 30% or more from the baseline. The surgeon was requested to withdraw muscle traction until the HR returned to the pre-reflex baseline level.However, if bradycardia persisted injection atropine 20µg kg-1 was administered intravenously.

Statistical analysis

Previous study by Ghai etal[6] was used to calculate the sample size. With an intention to achieve a 66% decline in the need for rescue analgesia in 30% children premedicated with a combination of oral midazolam with dexmedetomidine.90 subjects (45 in each group) was calculated using confidence interval of 95%.A total of 102 subjects were assessed for eligibility considering dropout rate of 10%.

Non-paired t-test and a Fisher's exact test was used to compare demographic data between the two groups. To determine the hemodynamic changes between and within the groups at various time intervals, two-way ANOVA was used. Non-parametric data were analysed using a Friedman test. The data is presented as descriptive values. Level of significance was defined at a p-value of <0.05.For secondary outcomes p-value was adjusted using a modified Bonferroni correction to account for multiple testing.

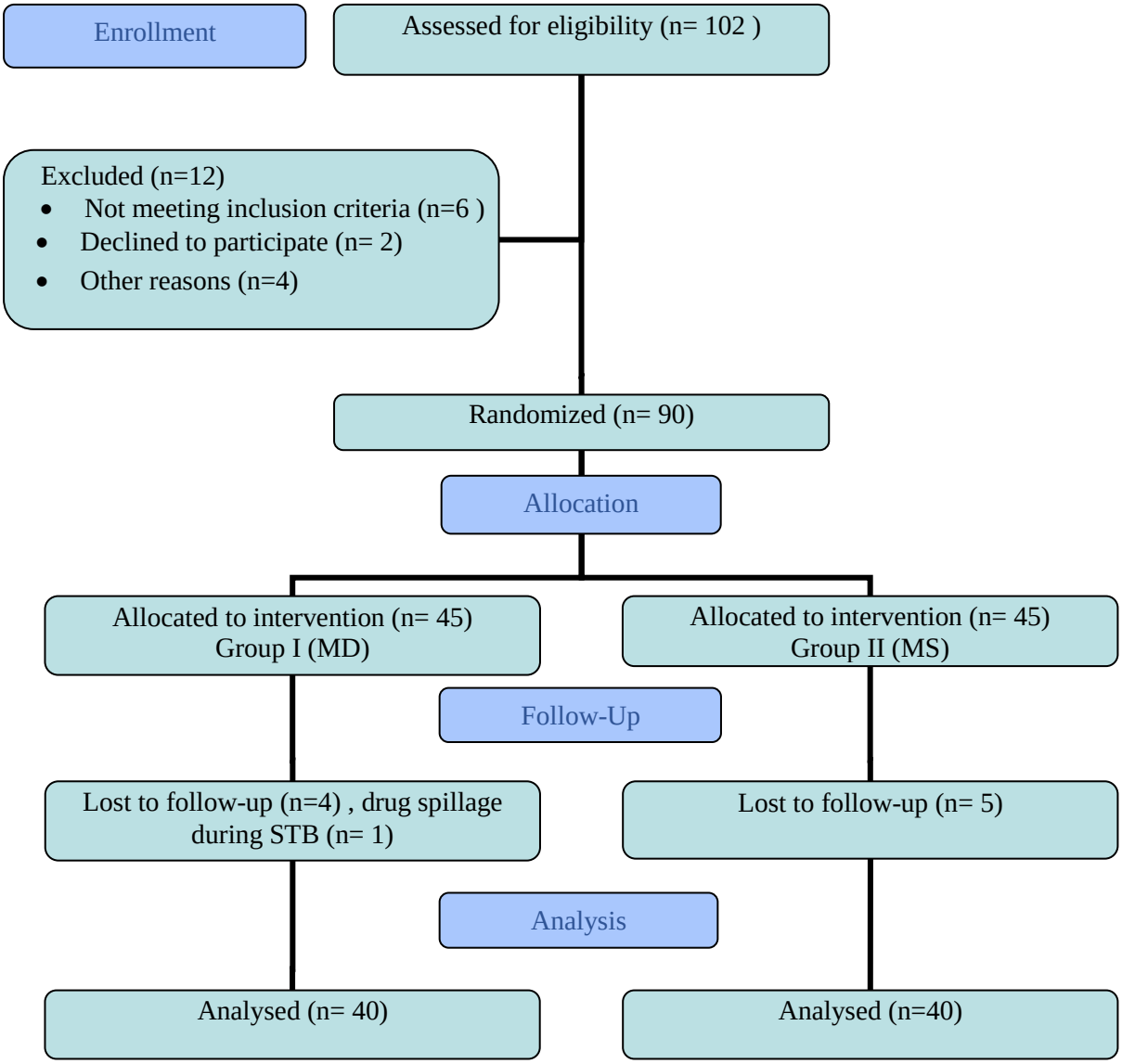
RESULTS

102 patients were assessed for eligibility out of which 12 were excluded. Hence, ninety patients were enrolled for the study. Ten enrolled patients were excluded because 1child had drug spillage during STB (Subtenon block) and others were lost to follow up.Finally,80 patients (n = 40 in each group)were analyzed(consort diagram).

Both groups were comparable for demographic characteristics as well as number of previous surgical interventions, premedication time and LMA insertion attempts(Table 1).The pre-sedation behavior, drug acceptability, parental separation and quality of mask acceptance evaluated showed no significant difference between the two groups(Table 2).

The MOAS scale showed comparable sedation in both groups at all-time intervals (Figure1).95% patients achieved MOAA/S ≤ 4 at 30 minutes in group MS and 90% children at the same time interval in group MD. In PACU, all the children were pain free at one hour in both the groups. The number of children having FLACC >3 who required first rescue analgesia in recovery were 15% in group MD in comparison to 27.5%with Group MS (Figure2).However, the need for second rescue was significantly higher in Group MS as compared to Group MD(Table3)

Consort - Flow Diagram



Intraoperatively no rescue analgesia was required in both the groups. Surgical condition as assessed by the operating surgeon were reported to be satisfactory in all the patients. There were no events of OCR in both groups. The baseline hemodynamic parameters were similar in both groups. But the intraoperative and postoperative HR was significantly lower in Group MD at all-time intervals(data not shown).The mean BP was similar in both the groups except in the immediate postoperative period when it was significantly lower in Group MD(data not shown).

PONV occurred more significantly in Group MS compared with Group MD. Parental satisfaction scores were satisfactory in both groups.

Table 1: *Patient demographic data*

Variable		MD (n=40)	MS (n=40)	P value
Age in Years*		3.77 (1-6)	3.42 (1-6)	0.348
Gender**	Male	27(67.5)	23(57.5)	0.356
	Female	13(32.5)	17(42.5)	
Weight in Kg*		14.5 (6-25)	13.7 (5-30)	0.479
Height in cm*		92.70 (70-110)	91.47 (68-110)	0.624
Previous Surgical Interventions**		16 (40)	10 (25)	0.346
ASA Physical Status 1or 2**		40(100)	40(100)	constant
Premedication Time* (min)		37.75±8.31	35.50±5.04	0.147
LMA Insertion Attempts**	1	39 (97.5%)	39 (97.5%)	1.000
	2	1 (2.5%)	1 (2.5%)	
Surgical Field Conditions** [Good /Fair/ Poor]		40/0/0	40/0/0	constant
Duration of Surgery*** (min)		19.5±3.89	19 ± 4.11	0.578
Duration of Anesthesia*** (min)		29.88± 4.36	29.18±4.21	0.468
Time to discharge readiness from PACU*** (min)		54.23±5.11	56.49±7.64	0.664

*Values in median (range), **number (percentage), *** mean ± SD

Table 2*: Presedation Behaviour, Drug Acceptability, Parental Separation and Mask Acceptance Score*

			MD (n= 40)	MS (n = 40)	P-value
Presedation Behavior[#]		Calm,Co-operative	16	19	0.755
		Anxious but reassurable	19	13	
		Anxious and not reassurable	3	7	
		Crying or resisting	2	1	
Drug Acceptability[##]	Oral	Good	10	15	0.352
		Fair	27	21	
		Poor	3	4	
	Intranasal	Good	03	03	0.566
		Fair	31	34	
		Poor	6	3	
Parental Separation [#]		Calm, Co-operative	35	35	1.000
		Anxious but reassurable	5	5	
		Anxious and not reassurable	0	0	
		Crying or resisting	0	0	
Mask Acceptance[#]		Calm, co-operative or asleep	20	24	0.437
		Moderate fear of the mask, cooperative with reassurance	20	15	
		Combative, crying	0	1	

[#] Mann Whitney/ [##] χ^2 test

Figure 1: *Bar diagram showing MOAA/S≤4 at various time intervals after premedication. More than 90% of patients achieved score ≤4 at 30 minute time period in both groups.*

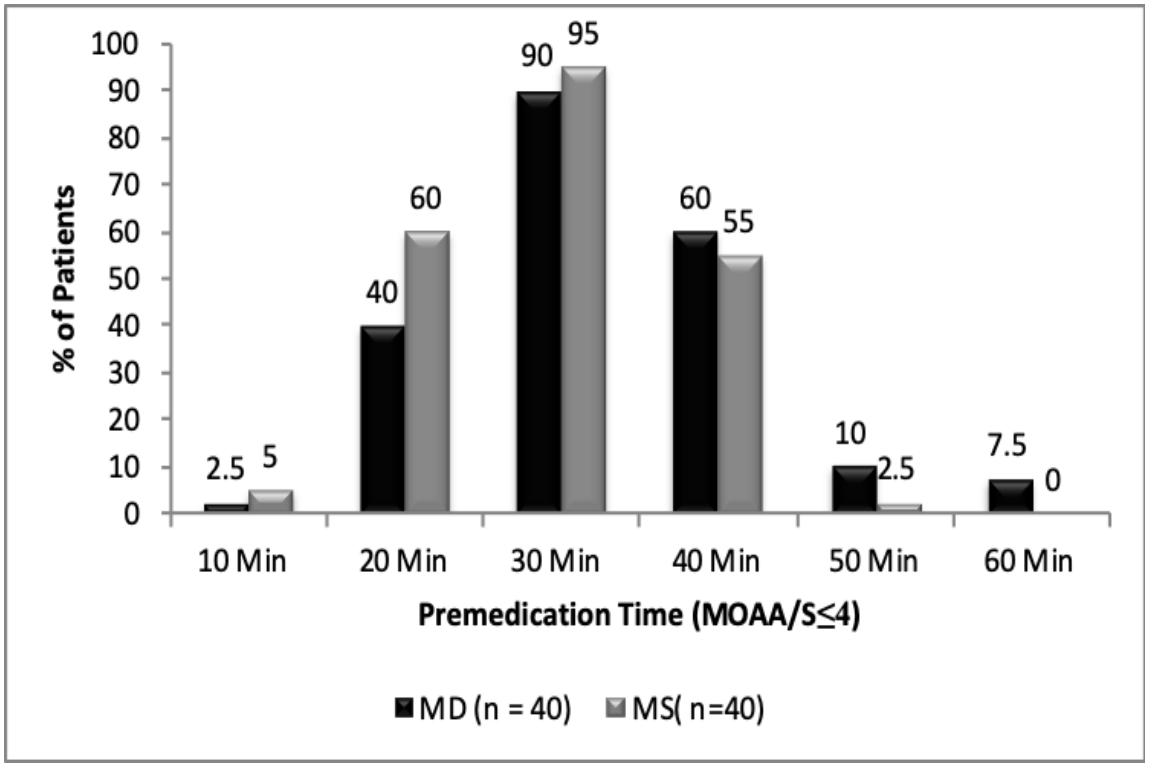


Figure 2*: Comparison of percentage of patients who required rescue analgesia during various time periods in the postoperative period.*

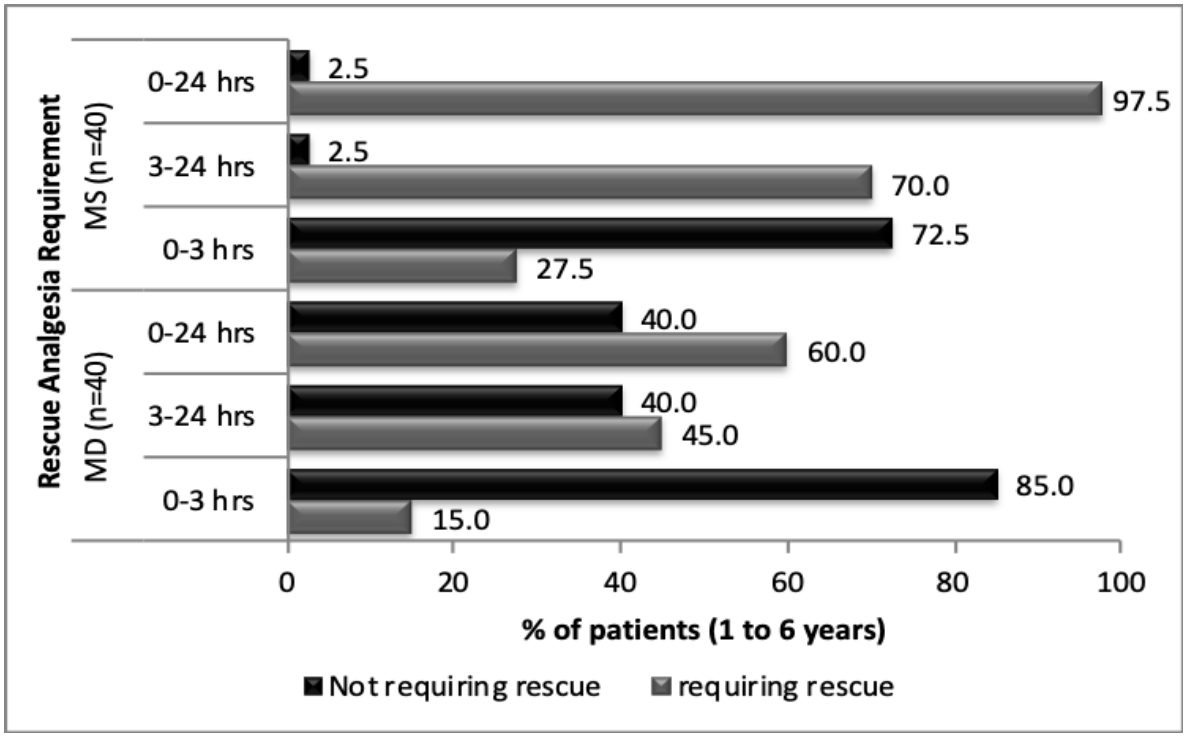


Table 3*: Post-operative need, of analgesia, frequency and time to first rescue analgesia*

			MD(n=40)	MS(n=40)	P value
Number of patients requiring rescue analgesia n(%)[##]	0-3 h (fentanyl)		6(15)	11(27.5)	0.172
	3-24 h (Paracetamol)		18(45)	28(70)	0.000*
Frequency of rescue analgesia n (%)[##]	0-3 h (fentanyl)	0	34(85)	29(72.5)	0.172
		1	6(15)	11(27.5)	
		2	0	0	
	3-24 h (paracetamol)	0	18(45)	1(2.5)	0.000*
		1	21(52.5)	24(40)	
		2	1(2.5)	15(37.5)	
Time to first rescue analgesia Median (Range) [$]	0-3 h [fentanyl]		10min[5-15]	5min[5-30]	1.000
	3-24 h (Paracetamol)		8.5 hours [7.8-9]	7 hours [7-8.5]	0.079

[$]T-test, [##]$\chi^2$

DISCUSSION

In the present study a combination of IND and oral midazolam and oral midazolam alone produced similar sedation. However, combined premedication provided better intraoperative hemodynamic stability and postoperative analgesia compared to routine oral midazolam premedication.

Midazolam produces its effect by facilitating gamma amino butyric acid (GABA) receptor binding in the cerebral cortex [7] whereas the primary site of action of dexmedetomidine is locus caeruleus which induces electroencephalographic activities similar to natural sleep.[1]IND is relatively easy to administer with bioavailability of 82% when compared to other non IV routes.[8]Akin *et al* studied the effectiveness of 1μg kg-1 IND versus 0.2mg kg-1 intranasal midazolam in children.[3]Authors reported that the time of onset of premedication was a limiting factor because for midazolam 45-60min duration is too long, as for dexmedetomidine this duration was be too short. It was observed that 1μg kg-1 IND produced satisfactory parental separation but the quality of mask induction was less satisfactory when compared with intranasal midazolam.

In another study,[9] combination of IND and buccal midazolam was associated with higher sedation success when compared to IND alone. In the current study, on combining IND and oral midazolam, 90% of the children had MOAA/S ≤4 at 30 minutes compared to 95% children who received only midazolam. Thus, anxiety of parental separation was equally managed in both the groups. The quality of mask induction was also suitable in all the patients in both the groups, except for one child in the combination group who had poor mask acceptance.

Optimal timing for administration of IND was studied by Yuen et al[10] who reported that onset time for IND is 25-30 minutes with median duration of sedation 85minutes.By combining intranasal DMT and oral midazolam, it was expected that onset of sedation will be earlier and prolonged with better tolerance to the mask induction. These goals were achieved in present study. A modest reduction in BP and HR is produced by α_2 agonists. n our study, mean blood pressure and heart rate in the MD group were comparatively on the lower side. However, the values were within 20% of baseline and none of the patients required pharmacological intervention. These results are consistent with previous studies.[11]The requirement of inhalation anesthetic agent as assessed by MAC was also less in MD group.

STB is a simple, effective and safe technique for large number of ophthalmic surgical procedures including cataract surgery.[12,13] In our study, STB was given to all patients before start of surgery. The rescue analgesia requirement at home was significantly less in combination group which can be attributed to sympatholytic and analgesic properties of dexmedetomidine and persistent analgesic effects of STB. Present study used ropivacaine 0.75% for STB, as it is less cardiotoxic than bupivacaine. Current study also reported no events of OCR in the intraoperative period. This observation is in accordance with previous studies.[14]

Besides having anxiolytic, analgesic and sympatholytic properties dexmedetomidine also reduces intraocular pressure contributing to its anti-emetic action.[15]Current study results demonstrate a significant decrease in incidence of PONV with MD combination. There was no difference between two groups with regard to adverse effects of drugs or events perioperatively.

Jia et al [16] studied the effects of two different doses of IND(1 and 2 μg kg-1) and oral ketamine (3 and 5 mg kg-1) concluding that 2μg kg-1 of IND and 3mg kg-1 of oral ketamine is an optimal combination for easy parental separation and intravenous cannulation. Authors also used remifentanyl and tramadol supplementation. However, polypharmacy of various drugs caused sedation leading to delay in removal of LMA. In yet another study,[11] comparing the effectiveness of STB with IV fentanyl for peri-operative pain relief,32% children in the fentanyl group required intraoperative ventilatory assistance because of apnea or hypopnea. To avoid this complication, we preferred assisted ventilation in all the children soon after the insertion of LMA. At the completion of surgery, all children were given 100% O_2 and LMA was removed once children achieved spontaneous and regular breathing. There was no delay in recovery of any children. We also avoided routine administration of opioids and all patients received analgesia in the form STB and IV paracetamol.

Strengths of this study are a vulnerable homogenous group of children undergoing cataract surgery, standardized anaesthesia protocol with adequate monitoring accomplished.STB was by given by same experienced surgeon in all the patients. Limitations are subjective assessment scales were used to measure anxiety and mask acceptance. Though, no psychometric data is available on these scales and these have been used successfully in previous studies. It may be essential to use more valid scales. To assess postoperative pain FLACC scale was used. Many studies have documented increased occurrence of emergence delirium after sevoflurane use despite absence of pain in children who had regional blocks [8].Emergence delirium scale like Paediatric Anaesthesia Emergence Delerium (PAED) scale are better tools for distinguishing pain from agitation.

In conclusion, premedication with combined intranasal dexmedetomidine (IND) and low dose oral midazolam is superior in decreasing postoperative analgesic requirements and incidence of PONV when compared to routine oral midazolam premedication alone in children requiring cataract surgery under general anesthesia. Further pharmacokinetic studies can be conducted to evaluate the safety and efficacy of intranasal premedicant drug mixtures in different study populations

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APPENDIX- 1

Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S):

6	Appears alert and awake, responds readily to name spoken in normal tone
5	Appears asleep but responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to noxious stimulus

APPENDIX- 2

Parental Separation Score (Four point scale):

Calm,cooperative	1
Anxious but reassurable	2
Anxious and not reassurable	3
Crying or resisting	4