

A randomized double blind comparative study of dexmedetomidine with midazolam for intranasal premedication in children undergoing ophthalmic surgery

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Keypoints

Anxiety and pain remain important issues in children during acute postoperative period immediately after emergence from anaesthesia. Dexmedetomidine was found to be better than midazolam when used as intranasal premedication in children posted for elective ophthalmic procedures as it produced stable heart rate and systolic blood pressure during preoperative period and reduced post-operative pain and post-operative analgesic requirement.

Abstract

Introduction

Anxiety and pain are important and frequently encountered issues in children especially during acute postoperative period immediately after emergence from anaesthesia. Additionally during ophthalmic surgical procedures, this is further compounded by inability to open one or both eyes post operatively. So, this study was planned to compare the efficacy of dexmedetomidine with midazolam used as intranasal premedication in children undergoing elective ophthalmic surgeries under general anaesthesia on post-operative analgesia, sedation and post-operative analgesic requirement.

Materials and Methods

60 Children aged 3 to 10 years, American society of anaesthesia (ASA) class I or II posted for elective ophthalmic surgery under general anaesthesia were randomly allocated into two groups (group D and L). Children in-group D received Dexmedetomidine 1 µg/kg intranasally approximately 30 mins before the start of sur-

gery. Children in-group M received intranasal midazolam 0.2 mg/kg approx. 30 mins before surgery.

Results

Children in group D had significantly lower values on objective pain scale when noted ½ hourly for first 2 hours post operatively. Likewise, Dexmedetomidine group has lower requirement of inj. Fentanyl. (07 doses in 06 children vs. 14 doses in 12 children)

Conclusions

Intra nasal dexmedetomidine premedication in children produced stable heart rate and systolic blood pressure during preoperative period and lowered the objective pain score with reduced analgesic requirement in post-operative period

Keywords: dexmedetomidine, midazolam, intranasal premedication, pediatric patients

Introduction

Anxiety and pain are important and frequently encountered issues in children especially during acute postoperative period immediately after emergence from anaesthesia.

sthesia. Additionally during ophthalmic surgical procedures, this is further compounded by inability to open one or both eyes post operatively. As a result, postoperative period becomes distressful for children, triggering tachycardia, nausea vomiting, excessive crying and/or violent struggle. This will further lead to increased requirement of analgesics and anxiolytics in the post-operative period. Many anxiolytics and analgesics drugs including fentanyl, midazolam, ketamine etc. which are being used as premedications, also help to reduce postoperative discomfort in children posted for elective ophthalmic surgeries.

Wilton and colleagues¹ were first to analyze the effectiveness of intranasal midazolam as preanaesthetic medication in children in 1988. Midazolam since then has been used in children for a number of elective surgical procedures as preoperative anxiolytic. Intranasal route is preferred as it has a fasted onset of action, compared to oral route due to direct absorption into systemic circulation^{2,3} and is not painful as intramuscular or intravenous routes. However, at higher doses, it may have side effects like excessive sedation, respiratory depression etc.⁴ Recently, alpha 2 agonists have been used successfully as premedication in children. These drugs are centrally acting sympatholytic which are devoid of any respiratory depression⁵. Dexmedetomidine is one such selective alpha 2 agonist, which is odorless and doesn't cause any mucosal stimulation when used intranasally. This drug causes anxiolysis and sedation and has been used intranasally for premedication in a number of studies⁶⁻⁸.

However very few studies are there that have studied the effects of intranasal dexmedetomidine premedication on post-operative pain and analgesic requirement. Therefore, we have conducted this study to compare the effectiveness of Dexmedetomidine with midazolam used intranasally in children undergoing elective ophthalmic surgeries under general anaesthesia on post-operative analgesia, sedation and post-operative analgesic requirement.

Materials and Methods

This double blind randomized study was conducted in a tertiary care institute in rural India. Before starting, the study approval was obtained from institutional ethics committee. Children undergoing elective ophthalmic surgery under general anaesthesia (squint surgery in our setting) were considered for this study. Inclusion criteria were age from 3 years to 10 years, American society of anaesthesia (ASA) class I or II, no active upper respiratory tract infection and no neurological deficits. Children less than 3 years or more than 10 years, ASA class III or more, refusing for intranasal drug administration, history of allergy to any drugs used in the procedure, were excluded from the study. Written informed consent was obtained from parents of all children before including them in the study.

All the patients were taken into per-operative room on the day of surgery. Pre-operative fasting status and fitness was ascertained. Parents accompanying the children were then explained about the study to be performed and the benefits and risks involved in the same. Written informed consent was obtained from all the parents. The children were then randomly allocated into 2 groups group D and group M using paper in the box technique. Children in-group D received Dexmedetomidine 1 µg/kg intranasally approximately 30 mins before the start of surgery. Similarly, children in-group M received intranasal midazolam 0.2 mg/kg.

For intranasal drug administration, children were made to lie in the lateral position and the calculated amount of drug was diluted in normal saline so that the final volume will be 1 ml. 0.5 ml of this solution was instilled into each nostril with the help of intranasal spray device. The anaesthesiologist responsible for administration of drug was different from the investigator (anaesthesiologist) responsible for further management of that patient who was unaware as to which drug has been administered to the patient. Vitals including heart rate, systolic and diastolic blood pressure and oxygen saturation were monitored in the pre-operative room before administration of

intranasal drug and every 10 mins afterwards, until the patient is shifted to operation theatre.

Intra-operatively, induction was done using 4-5% Sevoflurane with oxygen via Jackson Rees circuit. After induction, intravenous cannula (22G or 24 G) was secured and inj. Fentanyl 1 µg/kg & inj. Glycopyrolate 0.004 mg/kg was given to all patients. Endotracheal intubation was performed after achieving adequate muscle relaxation by non-depolarizing muscle relaxant (inj. Veccuronium 0.1 – 0.15 mg/kg i.v.). Intraoperative monitoring was done using pulse oximeter, non-invasive blood pressure, end tidal carbon dioxide and ECG. Intraoperatively all patients received intravenous infusion of paracetamol 15 mg/kg i.v. After completion of surgery neuro muscular blockage was reversed using inj. Neostigmine 0.35 – 0.5 mg/kg i.v. patients were then extubated and shifted to post anaesthesia care unit after achieving an Aldret score of 10.

Postoperative pain was assessed using objective pain scale⁹ after shifting the patients to post anaesthesia care unit and then every ½ hourly for 3 hours. This method has been used for pain assessment in children, is based on five parameters i.e. blood pressure compared pre-operative value; crying; movements; agitation; and verbalization of pain and each parameter is given a score of 0-2 depending upon severity. OPS score ranges from 0 to 10 with a score of 0 signifying no pain and 10 implying severe pain. Inj. fentanyl 0.5 µg/kg intravenously was used in children with OPS score ≥ 5 as rescue drug. Total no. of fentanyl doses used in both the groups was compared. Additionally, any undesirable effects like bradycardia, hypotension, excessive secretion etc. if any were also reported.

Data Handling

Investigator (different from the anaesthesiologist responsible for administering intranasal drug) did data collection for this study. Data was collected from 60 children aged 3 to 10 years, whose parents gave written consent for them to participate in this study, over a period of 8 months i.e. from February 2015 to October

2015. Data collected on a pre designed study performed, which were then analyzed by other two investigators involved in the study.

Sample Size Calculation

Based on previous studies^{7,8}, we compared the effect of intranasal dexmedetomidine pre medication with that of intranasal midazolam on objective pain scale 1 hour after surgery in children in a pilot study. We analyzed 10 children in each group, total 20 children. An objective pain score of three or less was considered as satisfactory. We found out that out of 10 children receiving intranasal dexmedetomidine 7 had an objective pain score of three or less (70% effective). While in midazolam group, only three children had an objective pain score of three or less (30% effective). So, with a difference of 40% considered to be statistically significant, we calculated the sample size required with $\alpha = 5\%$ and power of study 90%. We found out that 28 patients were required in each group. Therefore, in order to increase accuracy 30 children were included in each group.

Statistical Analysis

Data was collected on a Microsoft XL worksheet and analyzed using SPSS ® version 20 (Statistical Packages for the Social Sciences, Chicago, IL). Results were expressed either as mean \pm standard deviation or as numbers/percentages. Comparative analysis was done using unpaired t-test or Mann-Whitney test for quantitative data and chi square test for qualitative data. A P value of 0.05 or less was considered as statistically significant.

Results

In total 67 children were considered for this study. Out of these four children had nasal obstruction or running nose. So they were excluded from this study. Two children refused intranasal drug administration and one child had post-operative respiratory problem. So in total 60 children undergoing elective ophthalmic surgery were included in this study. They were randomly allocated into two groups with 30 children in each group. Demographic variables were compared in both groups and no statistically significant difference was noted (Ta-

ble 1). In addition, the mean duration of anaesthesia and surgical procedure were comparable in both groups (Table 1).

Demographic data of patients			
	Midazolam group (n=30)	Dexmedetomidine group (n=30)	P value
Age (yr)	5.4 ± 1.958	5.2 ± 1.750	0.6781
Sex (M:F)	19:11	13:17	
Weight (kg)	16.43±4.531	15.83±4.153	0.5949
Duration of anaesthesia (min)	33.37±5.605	32.83±5.478	0.7107
Duration of procedure (min)	25.07±5.638	23.73±5.356	0.3516

Table 1. Demographic data of patients

Pre-operative vitals i.e. heart rate, systolic blood pressure, diastolic blood pressure and oxygen saturation were statistically similar in both groups (Table 2).

Similarly, after 10 minutes of intra nasal drug administration no statistically significant difference was observed in vital parameters in both the groups (Table 2). However, after 20 minutes and 30 minutes, heart rate and systolic blood pressure were significantly less among children in group D as compared to those in group M (Table 2).

On comparing diastolic blood pressure and oxygen saturation in both groups, no statistically significant difference was observed. Intra operative period was uneventful for both the groups and no significant difference in vital parameters was observed.

Post operatively, children in group D had significantly lower values on objective pain scale when noted ½ hourly for first 2 hours post operatively though no significant difference was observed afterwards (Table 3). Likewise, Dexmedetomidine group has lower requirement of rescue analgesic i.e. inj. Fentanyl (07 doses in 06 children vs. 14 doses in 12 children) (Figure 1, Table 4).

No undesirable effects like bradycardia, hypotension, vomiting, excessive sedation etc. were noted in any patient during entire duration of study.

		Time interval (mins)	Midazolam group (n=30)	Dexmedetomidine group (n=30)	P-value
Heart rate	Before premedication	0	113.27 +7.080	114.57 + 5.557	0.4337
		10	109.13 +5.941	105 + 9.651	0.2298
	After premedication	20	106.57 + 5.673	97.73 + 6.736	<0.0001
		30	99.97 + 6.071	95.77 + 7.147	0.0351
Systolic Blood Pressure	Before premedication	0	112.3 + 6.753	109.73 + 5.570	0.0755
		10	108.93 + 6.286	107 + 6.223	0.3751
	After premedication	20	106 + 5.314	102.23 + 5.888	0.0041
		30	103.5 + 5.329	96.67 + 5.006	0.0015
Diastolic Blood Pressure	Before premedication	0	69.83 + 9.214	68.77 + 6.760	0.7002
		10	67.27 + 7.701	67.83 + 6.732	0.8760
	After premedication	20	67.1 + 6.105	66.77 + 6.479	0.6174
		30	67.17 + 7.149	65.03 + 4.279	0.2571
Oxygen Saturation	Before premedication	0	98.5 + 1.106	98.23 + 1.073	0.3545
		10	98.3 + 1.022	98.77 + 1.104	0.0952
	After premedication	20	98.6 + 1.163	98.83 + 1.085	0.4517
		30	97.93+1.048	97.9 + 0.8449	0.8337

Table 2. Comparison of Preoperative vitals of patients in Midazolam group and Dexmedetomidine

Objective Pain Scale			
Time (hrs)	Midazolam group (n=30)	Dexmedetomidine group (n=30)	P-value
½	3.83±1.21	3.13±1.48	0.0492
1	2.93±1.46	2.03±0.805	0.005
1 ½	2.86±1.28	2.1±1.29	0.0233
2	2.76±1.27	1.86±1.008	0.037
2 ½	1.73±0.639	1.63±1.03	0.654
3	2.93±0.91	2.86±1.43	0.83

Table 3. Comparison of Post-operative Objective Pain Scale in Midazolam group and Dexmedetomidine group

	Midazolam group (n=30)	Dexmedetomidine group (n=30)
The number (doses) of children requiring fentanyl as rescue analgesia medication	12 (14)	06 (07)

Table 4. Comparison of Post operative analgesic requirement in Midazolam group and Dexmedetomidine group

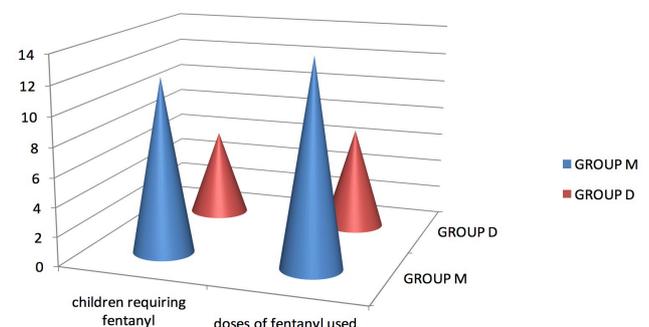


Figure 1. Post-operative analgesic requirement in group D and M

Discussion

Our study was done to evaluate and compare the efficacy of intranasal dexmedetomidine with midazolam on post-operative pain in children who underwent elective ophthalmic surgeries under general anaesthesia. We found that children receiving dexmedetomidine had lower objective pain scores when assessed every half hourly for first 2 hours post operatively. In addition, the total requirement of rescue analgesic was less in children receiving intranasal dexmedetomidine as compared to those receiving intranasal midazolam.

Dexmedetomidine has been found to be effective as intranasal premedication for anxiolysis in children compared to other drugs¹⁰. It is an alpha 2 agonist which acts at pre synaptic nerve terminals and causes inhibition of sympathetic outflow in central nervous system. It causes anxiolysis, sedation, without any respiratory depression, nausea or vomiting. Our study has found that dexmedetomidine reduces both heart rate and blood pressure in per-operative period though clinically significant bradycardia was not noted in any patient at intranasal dose of 1 µg/kg. This was due to central sympatholytic effect of dexmedetomidine. Dexmedetomidine premedication in children posted for elective surgeries has been found to be superior to midazolam in studies by Yuen et al⁶ and Sun et al¹¹. It preserves the respiratory function and this effect is particularly useful in children prone to obstructive sleep apnea. In addition emergence delirium noted in children after use of volatile anaesthetics. A study by Sun et al¹² has shown that dexmedetomidine reduces the incidence of emergence delirium and agitation in children after Sevoflurane anaesthesia.

Intra nasal route of administration of dexmedetomidine is preferred as no nasal irritation or burning sensation is associated with intranasal dexmedetomidine¹³. In addition, the absorption of intranasal dexmedetomidine is rapid with plasma concentration attaining peak value at around 38 mins (15-60 mins)¹⁴. Bioavailability of this intranasal drug is good and has been found to be 65 % (35-93%)¹⁵. Various recent studies have used different

doses of intranasal dexmedetomidine from 0.5 µg/kg to 3 µg/kg^{6, 15}. In current study, we have used intranasal dose of 1 µg/kg for dexmedetomidine, as it has been shown to produce effective anxiolysis without excessive sedation¹⁶⁻¹⁸. In addition, administration of this drug as of intranasal spray¹⁹ has been shown to be more effective compared to nasal drops. We have used intranasal spray for administration of both the drugs in our study.

Few studies done in recent past have studied the post-operative effects of dexmedetomidine premedication. In one study by Demuro et al, authors had found that in patients who have undergone spine surgery and have not achieved adequate analgesia from narcotics, dexmedetomidine could be an effective supplemental analgesic²⁰. Similarly, in a study by Dong Jian Ge et al. intra-operative dexmedetomidine had been shown to reduce post-operative pain scores and 24-hour morphine requirement in patients of abdominal hysterectomy²¹. Though both these studies have been done in adult population, in our study also we have found that dexmedetomidine premedication causes lower pain scores in children and decreases the post-operative requirement of narcotics.

In a meta-analysis by Ni et al²² use of dexmedetomidine has been found to be effective in preventing post-operative agitation in children. They also found it to be effective in reducing the incidence of severe post-operative pain, as well as reduces the requirement of rescue analgesic. Another meta-analysis by Schnabel et al²³ had also found that the use of intra-operative dexmedetomidine results in lesser post-operative pain scores and decreased post-operative analgesic requirement. However, in both these meta-analysis role of intra operative dexmedetomidine for post-operative analgesia has been investigated. In pediatric patients, pre-operative use of dexmedetomidine would be better as it satisfies the requirement of pre-operative anxiolysis as well. Therefore, we have studied the effect of intranasal dexmedetomidine on post-operative analgesia and narcotic requirement in children.

Similarly, during the post-operative period children in dexmedetomidine group had lower objective pain scores when measured at 30 mins interval for first 2 hours. Ghali et al⁷ reported similar finding. Dexmedetomidine has been shown to have a half-life of about 2 hours²⁴. This might have resulted in decreased objective pain scores and lower consumption of rescue analgesic in children who received dexmedetomidine as compared to midazolam group. No significant post-operative complication like bradycardia, hypotension, and excessive sedation were noted in our study.

There were certain limitations in present study. Firstly, the sample size used for this study was small. That may have resulted in fragility i.e. small changes in number of patient results in large changes in P values²⁵. Secondly, there is no commercially available standardized formulation of intranasal dexmedetomidine. Use of tailor made drug delivery system may cause variability across clinical trials due to different bioavailability. This may adversely affect the accuracy of results. Also without this, the relative cost effectiveness of both formulation could not be compared. Thirdly, many other effects of dexmedetomidine like those on post operative shivering, emergence agitation were not studied in the present study. This study was designed to specifically compare the efficacy of intranasal dexmedetomidine with midazolam so the sample size just sufficient for that purpose was calculated and studied. So further studies with larger number of patients are required to establish the role of dexmedetomidine premedication for post-operative analgesia in children.

Conclusion

In conclusion, intra nasal dexmedetomidine premedication in children posted for elective ophthalmic procedures caused stable heart rate and systolic blood pressure during preoperative period and lowered objective pain score with reduced analgesic requirement in post-operative period as compared to intranasal midazolam.

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