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Comparison of Efficacy of Premedication between Dexmedetomidine and Midazolam Intranasal for the Prevention of Emergence Delirium in Children Undergoing Ophthalmic Surgery

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Abstract

Objective: Emergence delirium (ED) is a condition that can occur when a child recovers from anaesthesia uncomfortably. ED can potentially injure children and indirectly discomforts parents. Various interventions were carried out to reduce ED, but there is no specific standard that has been established to prevent ED. Dexmedetomidine and midazolam are said to be effective in reducing ED. This study aims to determine the effectiveness of intranasal dexmedetomidine premedication compared to intranasal midazolam to prevent ED in children undergoing eye surgery.

Methods: This study was a double-blinded randomised clinical trial. Paediatric patients aged 1-12 years with physical status ASA 1 and 2 who underwent eye surgery under general anaesthesia using sevoflurane inhalation were included in the study. There were 64 children obtained by consecutive sampling who underwent eye surgery in our institution between February and May 2019. The subjects were then randomised into the dexmedetomidine group and the midazolam group. Effectiveness was assessed from ED events, recovery time and post-premedication desaturation events. Data analysis was performed using Chi-square test and Mann–Whitney test.

Results: ED incidence in the dexmedetomidine group was 11.18% compared to 28.12% in the midazolam group ($P = .109$). The recovery time was found to be at a median of 6 minutes for both groups, and no desaturation was found in either group.

Conclusion: There is statistically no significant difference between the effectiveness of intranasal dexmedetomidine and midazolam premedication 30 minutes before induction to prevent ED occurrence in children undergoing eye surgery.

Keywords: Emergence, delirium, dexmedetomidine, midazolam, eye surgery

Introduction

Several conditions are known to be related in the process of a child emerging from anaesthesia such as post-anaesthesia excitement, delirium and agitation. Emergence delirium (ED) may occur at any age but is found most commonly between ages 2 and 6 years old.[1] In our institution, the incidence of post-operative ED in children was 39.7%.[2] Upon uncomfortable emergence, external stimulus triggers an excitative state. This excitative state upon emergence may potentially injure the patient, such as reopening the surgical wound and displacement of the intravenous catheter, which in turn leads to the administration of more sedative or analgesic drugs leading to a prolonged length of stay. This state of agitation may also, in turn, cause discomfort and displeasure from the child's guardian or parents. Several studies have aimed to prevent or reduce the incidence of ED. Currently, some of the proposed methods include premedication with propofol, fentanyl, clonidine, dexmedetomidine, midazolam, ketamine and magnesium sulphate.[3-7] Midazolam is an anxiolytic, sedative agent with amnestic effects. It has been used for premedication in our institution. Midazolam can be administered orally, intranasally and intravenously. However, premedication with midazolam is associated with the risk of respiratory depression and not effective to

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reduce the incidence of ED.[8] On the contrary, dexmedetomidine is a potent, selective and specific α2 agonist, which exhibits a sedative and analgesic effect with no risk of respiratory depression and has been used as premedication in children. Dexmedetomidine is known to reduce the rate of ED and prevent post-operative nausea and vomiting.[9] Paediatric patient might present to the operating theatre without any IV access; hence, alternative drugs' routes should be in consideration. Intranasal route offers some advantages, including ease of administration and rapid onset. Hence, intranasal can be considered as an alternative whenever intravenous route is not available.[10,11] This study aims to determine the effectiveness of intranasal dexmedetomidine premedication compared to intranasal midazolam to prevent ED in children undergoing ophthalmic surgery.

Methods

This study was a double-blinded randomised clinical trial. After approval from the Ethical Committee for Medical Research, Faculty of Medicine Universitas Indonesia, Mangunkusumo Hospital, children aged 1-12 years old undergoing ophthalmic surgery with inhalational sevoflurane were enrolled in the study between February and May 2019. Sample size was calculated based on an expected clinical difference of 30%, with power of 84%, baseline incidence 0.39 (2) and alpha error 5%. Hence, the calculated sample size was 64. Inclusion criteria were physical status ASA 1 and 2, aged 1-12 years old and informed consent from parents of child. Exclusion criteria include plan of post-operative care in the Paediatric Intensive Care Unit, patients with psychologic or neurologic conditions, growth and development disorders, under sedative drugs therapy, history of allergy toward dexmedetomidine or midazolam, history of malignant hyperthermia and history of familial malignant hyperthermia and difficult airway.

Sample was obtained by consecutive sampling, and children scheduled for ophthalmic surgery fulfilling the inclusion criteria were enrolled in the study 1 day prior to surgery. Simple randomisation was performed, and each subject was assigned to either the dexmedetomidine group or the midazolam group. The randomisation result was placed inside a nontransparent envelope by members of the research team not involved in data collection. On the day of the surgery, age, gender, body weight, diagnosis, type of surgery and physical ASA status were recorded. All of the children enrolled in the study were then accompanied by their parents/guardian to the operating room in order to reduce preinduction anxiety.

Main Points

- Premedication of dexmedetomidine and midazolam intranasal are effective in prevention of emergence delirium compared to literature, neither are superior.
- The rate of emergence delirium out of 64 subjects was 23%.
- Neither premedication of dexmedetomidine or midazolam lengthened emergence time.

Envelopes with the result of the randomisation were then opened by the anaesthesia team in the operating room, not involved with the research team and without the presence of the research team. The children were then given premedication with dexmedetomidine 1 mcg kg^{-1} BW intranasal or midazolam 0.1 mg kg^{-1} BW according to the randomisation results. The research team then records preinduction anxiety using the preanesthetic behaviour scale.

Induction was then performed using sevoflurane gas 6-8 vol%. Monitoring devices (pulse oximetry, ECG, NIBP and capnograph) were then placed. All patients were then administered fentanyl 1 mcg kg^{-1} IV and atracurium 0.2 mg kg^{-1} IV, and ventilation with 100% oxygen was then given for 2-3 minutes. Supraglottic airway device (SAD) was then placed. Anaesthesia was maintained with sevoflurane 2 vol%. Ventilation was given with a target tidal volume of 6-7 mL kg^{-1} and $ETCO_2$ of 35-45 mmHg. MAP and pulse rate were maintained at a range of 20% from baseline, and an extra dose of fentanyl 1 mcg kg^{-1} IV was given upon signs of intraoperative pain. Atracurium was given 0.2 mg kg^{-1} IV every 30 minutes. Upon the completion of surgery, sevoflurane was administered at 0.5 vol%. Ondansetron 0.1 mg kg^{-1} IV and paracetamol 10 mg kg^{-1} IV were then given as an antiemetic and analgesic. SAD was then removed on the return of spontaneous breathing with tidal volume 6-7 mL kg^{-1} and $ETCO_2$ 35-45 mmHg. The end of anaesthesia marked with the cessation of sevoflurane and removal of the SAD was recorded. The child was then transferred to the PACU as soon as the transfer criteria were fulfilled. The transfer criteria included clear and patent airway without any manoeuvre, adequate ventilation and oxygenation and hemodynamic stability. Time to emergence was recorded from the end of anaesthesia until the child is able to open their eyes spontaneously and able to follow simple instructions. ED was then assessed by the research team, still blinded to the intervention using the Paediatric Anaesthesia Emergence Delirium (PAED) scale. ED was diagnosed it the child scored $\geq$10 on the PAED scale.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Normally distributed data were analysed using unpaired t-test. Not normally distributed data were analysed using the Mann–Whitney test.

Results

Data were collected between February and May of 2019 in [blinded]. Sixty-six subjects fulfilling the inclusion criteria

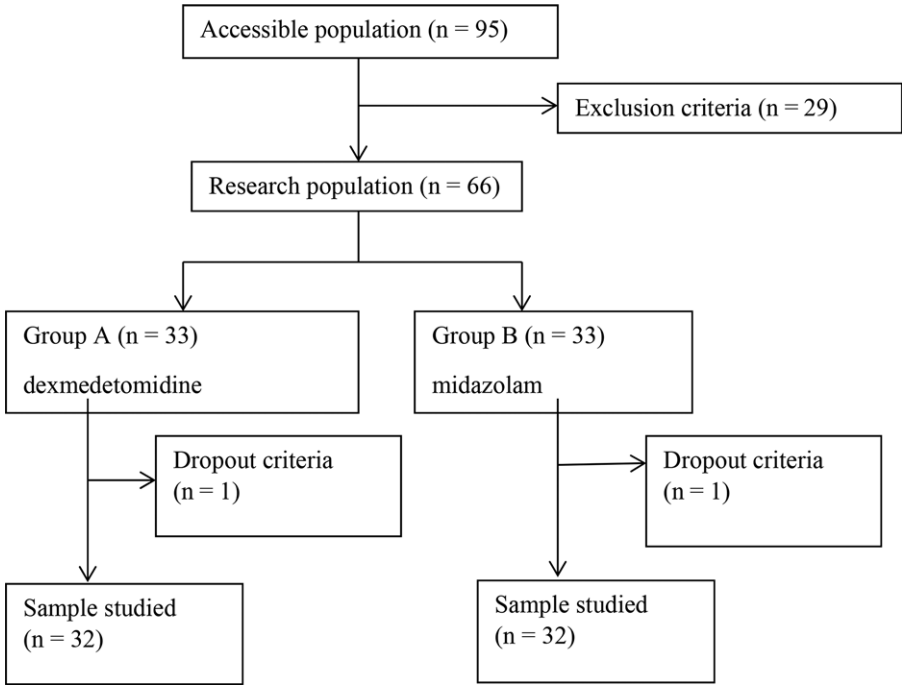

Figure 1. Research scheme.

Table 1. Study Population Characteristic

Variable	Group	
	Dexmedetomidine (n = 32)	**Midazolam (n = 32)**
Gender		
Male	16 (50.0%)	15 (46.8%)
Female	16 (50.0%)	17 (51.2%)
Age (years)	3.00 (1.00-9.00)	5.00 (1.00-10.00)
Body weight (kg)	13.00 (6.00-32.00)	18.00 (8.00-35.00)
ASA		
1	11 (32.4%)	14 (42.4%)
2	23 (67.6%)	19 (57.6%)
Inhalational anaesthesia duration (minutes)	60.17 ± 17.88	58.33 ± 19.31
Fentanyl dose (mcg $kg^{-1} h^{-1}$)	1.5 (0.84-3.6)	1.56 (0.66-3.60)
PAB score		
1	12 (40.6%)	14 (43.8%)
2	15 (46.9%)	10 (31.3%)
3	4 (12.5%)	8 (25.0%)

Categoric variable presented in (%), normally distributed numeric variable presented in mean ± standard deviation, not normally distributed numeric variable presented in median (min – max).

were included in the study. Subjects were divided into two groups based on randomisation. Group A received premedication with intranasal dexmedetomidine, while group B received premedication with intranasal midazolam (Figure 1).

Study population characteristics recorded include gender, age, body weight, ASA physical status, inhalational anaesthesia duration, fentanyl dose and Paediatric Anaesthesia Behaviour (PAB) score (Table 1).

Table 2. Comparison of Emergence Delirium Between Dexmedetomidine and Midazolam Groups

	ED				CI 95%	
	No (n = 52)	Yes (n = 12)	*P* value	RR	Min	Max
Group						
Dexmedetomidine	28 (87.50%)	4 (11.18%)	0.11	1.21	0.95	1.55
Midazolam	23 (71.87%)	9 (28.12%)				

Chi-square test.

Table 3. Comparison of Recovery Time and Desaturation

	Groups		
Variable	Dexmedetomidine (n = 32)	Midazolam (n = 32)	*P*
Recovery time*	6.00 (4.00-12.00)	6.00 (4.00-9.00)	.084
Desaturation†			
Yes	0 (0%)	0 (0%)	–
No	32 (100%)	33 (100%)	

*Mann–Whitney test.
†Chi-square test.

Rate of ED in the study was found to be 20% (n = 13). Out of the 13 subjects that experienced ED, four were from the dexmedetomidine group and nine from the midazolam group. A chi-square test was performed, and the difference was found to be not significant ($P = .11$) (Table 2).

Median value of recovery time in both groups was found to be the same, 6 (4.00-12.00) in the dexmedetomidine group and 6 (4.00-9.00) in the midazolam group. There was no statistically significant difference in recovery time of both treatment groups ($P = .084$) (Table 3). No case of desaturation was reported in either groups.

A Spearman correlation test was performed to study the relationship between PAB score and PAED score. The result was found to be not statistically significant ($R = 0.11$, P value = .38). Strength of correlation was very weak, the higher the PAB score the higher the PAED score.

Discussion

This study showed that intranasal dexmedetomidine premedication did not superior compare to intranasal midazolam to prevent ED in children undergoing eye surgery. All 64 children were included in the study. As seen in Table 1, study characteristics of both groups were found to be similar. Multiple studies have identified the preschool age (2-5 years) as the age group with the highest incidence of ED.[1,2,5] The median of the midazolam group was 5 years old, and the median of the dexmedetomidine group was 3 years old. Both groups had dominantly children in the preschool age group. It is hypothesised that preschool children cope poorly toward new environments, while physiologically, neurotransmitter function is still immature, hence contributing to the higher rate of ED in preschool children.[10]

Physiologic conditions such as hypoxemia, hypercapnia and hypotension were identified as confounding factors. These factors were controlled during anaesthesia management. The inclusion criteria also aimed to select subjects with relatively normal preoperative physiologic conditions. Intraoperative physiologic changes such as haemodynamics, oxygenation and ventilation were not studied, as anaesthesia will certainly have an effect. Drastic physiologic changes during anaesthesia are recognised as an emergency and a dropout criterion.

Pain is known to elicit an agitated state which mimics ED; however, ED also occurs in painless procedures. ED is not caused by pain; hence, opioid administration does not effectively prevent ED.[1,2,6] In this study, the level of pain was found to be uniform, marked by the amount of fentanyl administered. A study by Lewis et al. identified that ophthalmologic procedures had the highest rate of ED (28%) compared to urologic, orthopaedic and general surgery

procedures. The high rate of ED in ophthalmologic procedures is thought to be attributed to a disturbance in vision post procedure that causes agitation.[8]

Preoperative anxiety is another factor thought to be attributed to the rate of post-operative ED. Children with poor adaptation ability marked with preoperative anxiety are known to have a higher chance of post-operative reactive or situational agitation, especially as the child awakes in an unfamiliar setting.[10-12] A study by Aono et al.[13] in children undergoing circumcision showed that the rate of post-operative ED was found to be higher in children with preoperative anxiety. Preoperative anxiety was measured with the Paediatric Anaesthesia Behaviour (PAB) scale. Preoperative anxiety between the two treatment groups was found to be not significantly different. This finding is in accordance with a study by Bergendahl et al., which found that both midazolam and dexmedetomidine exhibit a similar sedative effect even though exerting its effect on different pathways.[13] The residual sedative effect or reduction in anxiety brought upon by dexmedetomidine or midazolam are thought to reduce the rate of post-operative ED.[8]

The rate of ED in literature varies from 10 to 80%. While a study conducted by Wijaya[2] in our centre reported the rate of ED in patients going general inhalational anaesthesia was found to be at 39.7%. In this study, the rate of ED was observed at 11.1% (4/32) in the dexmedetomidine group and 28.1% (9/32) in the midazolam group. The difference was found to be not statistically significant. Neither was found to be superior to the other in regard to reducing the rate of ED. However, when compared to the rate of ED in our centre, administration of dexmedetomidine or midazolam exhibited a lower rate of ED.

Premedication with dexmedetomidine exerts an anxiolytic, sedative and analgesic effect, which in turn reduces stress during intubation and extubation.[8] Dexmedetomidine inhibits its spontaneous activity of the central monoaminergic system, pivotal to sleep and arousal, hence exerting a natural sleep sedative effect. A study by Bergendahl et al.[14] concluded that dexmedetomidine reduced the incidence of delirium after inhalational sevoflurane. It is hypothesised that sevoflurane reduces production of noradrenaline in the locus coeruleus which in turn increases inhibitory stimulation threshold in the form of gamma-aminobutyric acid (GABA).

The use of midazolam to prevent postoperative ED is known to be controversial. Some studies have shown the effectiveness of midazolam in reducing ED, while some studies have shown no effect, even an increase in the rate of ED attributed to midazolam. It is hypothesised that midazolam may reduce the rate of ED by reducing anxiety before the procedure and residual effect of midazolam post-sedation.[8] However, a study by Breschan et al.[8] showed that there was no difference in post-operative behaviour between subjects who received dexmedetomidine and those who did not. Another study by Cohen et al.[4] found that children who received midazolam premedication had a nine times higher rate of ED compared to children who did not receive midazolam. Midazolam's high affinity toward GABA receptor is thought to induce delirium as midazolam impairs acetylcholine function.

There was no significant difference between emergence time in both groups (Table 3). In a previous study in our centre, the average emergence time on a variety of procedures was found to be at 7.8 minutes.[15] At 6 minutes for both treatment groups, emergence time between those given premedication and those who were not does not differ significantly. Emergence time is known to be positively correlated with anaesthesia duration, the longer the duration the longer the emergence time. The duration of anaesthesia in both groups was similar, hence removing possible bias.

PAB and PAED were found to be not statistically correlated. The correlation was positive, the higher the PAB score the higher the PAED score, albeit not statistically significant. Results found in this study differ from Wijaya et al.[2] which found that the higher the preoperative anxiety the higher the rate of ED. Children that are more emotional, impulsive and adapt poorly are known to have higher risk of ED.[13,16] In our study, PAB was assessed after administration of premedication with dexmedetomidine or midazolam. As PAB was assessed after premedication, it is a possibility that its anxiolytic properties have taken effect, therefore reducing the strength of association between PAB score and PAED score. The limitation of this study was the uncertainty of premedication time. The authors set the premedication time as 30 minutes before induction, to give enough time for the drugs to be at the peak level. However, the premedication time could not always under control and might influence the effect of the drugs. There were no control group in this study also limit the comparison data regarding the incidence of ED.

In conclusion, neither dexmedetomidine or midazolam intranasal were superior to each other in reducing the rate of ED. When compared to a previous study in our centre, the rate of ED was found to be lower. Time to emergence in both groups was not significantly different, and there was no incidence of desaturation in both treatment groups.

Ethics Committee Approval: Ethical committee approval was received from the Universitas Indonesia (1333/UN2.F1/ETIK/2018). Clinical trial registration number: NCT04263844.

Informed Consent: Verbal informed consent was obtained from all participants who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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