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Comparison of pre-extubation propofol and midazolam to prevent emergence agitation in children—a prospective randomized study

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Abstract

Background: Emergence delirium is one of the most common and troublesome complications seen after inhalational anesthesia, with an estimated 20–80% incidence rate. It can lead to an increase in mortality, morbidity, and hospital stay, which indirectly reflects a major economic burden. The aim of our study is to compare the effect of propofol and two different doses of midazolam to prevent emergence agitation in children given 5 min before extubation. Seventy-five ASA (American Society of Anesthesiologists) Physical Status I–II patients aged 2–14 years who were scheduled for elective surgeries under general anesthesia were included in the study. Patients in the study groups were randomized into three groups 25 in each group; group P (propofol of 0.5 mg/kg iv), group ML (midazolam low dose of 0.03 mg/kg iv), and group M (midazolam of 0.05 mg/kg iv) given 5 min before extubation. The primary objective was to study the effect of propofol and two different doses of midazolam for the prevention of emergence agitation in children. The secondary objective was to observe the complications like bronchospasm, laryngospasm, persistent cough, and desaturation in pediatric patients.

Results: The time taken for emergence from anesthesia after surgery in the propofol group was 5.11 ± 1.223 min and in the group midazolam low dose and midazolam time taken was 8.53 ± 2.326 min and 12.45 ± 2.145 min, respectively, and was found to be statistically significant. The incidence of delirium observed with a Cole score of >3 was seen in 14 (56%) patients in group P, 7 (28%), and 6 (24%) patients of groups ML and M, respectively.

Conclusions: Midazolam in low doses given before extubation is effective in preventing the emergence delirium during the postoperative period in pediatric patients without delay in recovery during general anesthesia.

Keywords: Emergence delirium, Extubation, General anesthesia, Midazolam, Propofol

Background

Emergence delirium (ED) is described as a psychological disturbance in the postoperative period. It is observed in about 25–80% of children who underwent general anesthesia (Lee et al. 2010). Clinical manifestations range from restlessness, involuntary physical movements, irritability, crying, etc. ED even though a self-limiting condition usually lasts for 1–2 h postoperatively, and children will become difficult to manage in the unfamiliar surroundings in the post-anesthesia care unit (PACU). A calm and cooperative child would be ideal for maintaining, intravenous lines, surgical site dressings, drains, urinary catheters, epidural/regional anesthesia catheters, etc. Various factors affect the occurrence of ED which includes the age, gender, ASA (American Society of Anesthesiologists) physical status, and type of surgical/anesthesia technique (Aouad et al. 2007). ED can lead to increased mortality, morbidity, and increase in hospital

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stay, which indirectly reflects a major economic burden (Cho et al. 2014).

This prospective randomized study was done to study the incidence and severity of emergence delirium in pediatric patients who underwent elective surgeries under general anesthesia. The primary objective was to study the effect of propofol and two different doses of midazolam for the prevention of emergence agitation in children. The secondary objective was to observe the complications like bronchospasm, laryngospasm, persistent cough, and desaturation in pediatric patients.

Methods

The prospective randomized study was done at a tertiary care teaching hospital after obtaining institutional ethical committee approval IEC No-EC/313/2018-19. The study was conducted over a period of 1 year between October 2018 and October 2019. Written informed consent was obtained from the parents/guardians for the study. Seventy-five ASA Physical Status I–II patients aged 2–14 years who were scheduled for elective general surgical procedures such as appendicectomy, herniotomy, and tonsillectomy under general anesthesia were included in the study. Patients with congenital anomalies, allergy to propofol, or any neurologic disorders or refusal to give consent were excluded from the study. Patients in the study groups were randomized using a computer-generated random number table into three groups of 25 patients in each group, and drugs were administered intravenously (i.v); group propofol (group P) 0.5 mg/kg iv, group midazolam (group ML) low dose of 0.03 mg/kg iv, and group midazolam (group M) 0.05 mg/kg iv given 5 min before extubation.

All patients underwent a thorough clinical examination the day before surgery. Relevant laboratory and radiological investigations were done depending on the individual patient requirements according to institutional protocol. All patients were scheduled for surgeries in the morning hours and followed standard fasting guidelines. An intravenous cannula was secured in the preoperative room. Basal parameters such as the heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SpO_2) were monitored in the preoperative room. Monitors were attached to the operating room. General anesthesia was administered with a standard anesthesia protocol for all patients. Premedication was given with midazolam of 0.03 mg/kg iv, atropine of 0.01mg/kg iv, ondansetron of 0.15 mg/kg iv, and fentanyl of 2 mcg/kg iv. The patients were induced with propofol of 3 mg/kg iv, and to facilitate intubation, atracurium of 0.5 mg/kg iv was given. Patients were maintained using oxygen, nitrous oxide (FiO_2 0.50), 1–3% sevoflurane, and inj atracurium with controlled ventilation. Intraoperatively, vital parameters were recorded. Five minutes before extubation depending on the allocated groups, the patients received study drugs accordingly, i.e., group P (propofol of 0.5 mg/kg iv), group ML (midazolam low dose of 0.03 mg/kg iv), and group M (midazolam of 0.05 mg/kg iv). At the end of the surgery, neuromuscular blockade was reversed with iv neostigmine 0.03 mg/kg and atropine 0.01 mg/kg. The patients were evaluated for postoperative agitation using the Cole agitation scale (Table 1) 10 at 10 min, 20 min, 30 min, 45 min, 1 h, and 2 h postoperatively. Patients having a score of >3 were considered to have ED. The heart rate, mean arterial blood pressure, oxygen saturation, respiratory rate, and side effects were recorded in PACU. Postoperative pain was assessed using FLACC Score (face, legs, activity, cry, consolability). Rescue analgesia was given with inj. fentanyl of 0.5mcg/kg iv if FLACC score is found to be >5. Complications like bronchospasm, laryngospasm (characterized by an inability to ventilate the patient's lungs and requiring either administration of continuous positive pressure or a neuromuscular blocking agent to restore ventilation), persistent coughing (duration longer than 15 s), desaturation (SpO_2<95%), reintubation, and postoperative bleeding were noted. The patients were observed in the PACU for 12 h Fig 1.

Statistical analysis

The calculated sample size was 60 to get a two-tailed significance level of 5% and 80% power of detection of an occurrence of emergence delirium of 30%. A total of 75 patients were included in the study with three groups of 25 patients each. Demographic and clinical characteristics were presented as numbers and percentages. Continuous variables were expressed as the mean and standard deviation (SD). Paired t test, chi-squared test, Fisher's exact test, ANOVA, and Mann-Whitney U test were used for data analysis. A p value of <0.05 was considered statistically significant. SPSS 22 version (IBM SPSS Statistics, Somers NY, USA) software was used for statistical analysis.

Results

All three groups were comparable with no statistically significant difference in terms of demographic profile parameters like age, gender distribution, weight, and duration of surgery (Tables 2 and 3). The time taken for emergence from anesthesia after surgery was 5.11 ± 1.223 min, 8.53 ± 2.326 min, and 12.45 ± 2.145 min in groups P, ML, and M, respectively, and was found to be statistically significant (p<0.001).

The incidence of delirium with a Cole score of >3 was observed to be 14 (56%), 7 (28%), and 6 (24%) in groups P, ML, and M, respectively, in PACU and was found statistically significant among the study groups (Fig. 2). The

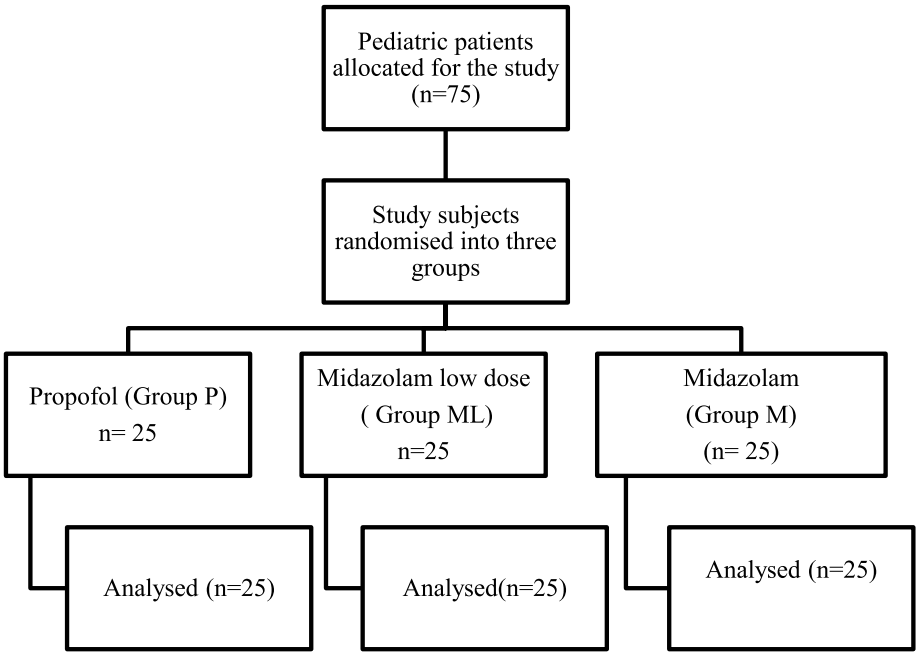

Fig. 1 Consort flowchart

Table 1 Cole scoring system for emergence agitation

Score	Behavior
1	Sleeping
2	Awake, calm
3	Irritable, crying
4	Inconsolable crying
5	Severe restlessness, disorientation

intergroup comparison of the incidence of ED between group P and group ML (p=0.04) and comparison between group P and group M (p=0.02) was found to be statistically significant. There was no statistically significant difference between the incidence of ED in group M and ML (p=0.747).

Cole's score at 10 min, 20 min, and 30 min postoperatively were significantly less (p<0.001) in group M and group ML compared to group P. The difference was not statistically significant at 45 min, 1 h, and 2 h (Tables 4

Table 2 Demographic data and duration of surgery

Parameters	Group P (propofol)	Group ML (midazolam low dose)	Group M (midazolam)	*P* value
Age (years)	5.76 ± 2.66	5.36 ± 2.018	6 ± 2.14	0.9802
Gender (male/female)	14/11	15/10	14/11	0.532
Weight (kg)	14.26 ± 5.008	13.96 ± 3.28	13.13 ± 5.253	0.9080
Duration of surgery (min)	59.6 ± 32.75	52.6 ± 33.138	54.8 ± 28.403	0.725

Values are presented as mean±SD, *p value <0.05 statistically significant

Table 3 Emergence time and emergence delirium

Parameters	Group P (propofol)	Group ML (midazolam low dose)	Group M (midazolam)	*P* value
Emergence time (mins)	5.11 ± 1.223	8.53 ± 2.326	12.45 ± 2.145	<0.001*
Incidence of emergence delirium	14 (56%)	07 (28%)	06 (24%)	

Values are presented as mean±SD, number of patients (%), *p value <0.05 statistically significant

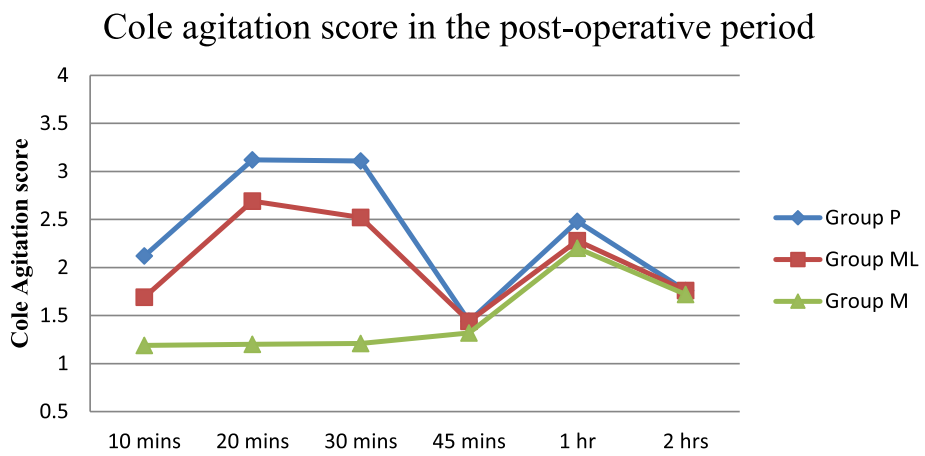

Fig. 2 Cole agitation score in the postoperative period

Table 4 Cole agitation score in the postoperative period

Cole score	Group P (propofol)	Group ML (midazolam low dose)	Group M (midazolam)	*P* value
10 min	2.12 ± 1.343	1.69 ± 1.598	1.19 ± 0.473	<0.001
20 min	3.12 ± 0.342	2.69 ± 0.596	1.2 ± 0.472	<0.001
30 min	3.11 ± 0.442	2.52 ± 0.153	1.21 ± 0.332	<0.001
45 min	1.44 ± 0.711	1.44 ± 0.711	1.32 ± 0.556	0.762
1 h	2.48 ± 0.653	2.28 ± 0.808	2.2 ± 0.50	0.315
2 h	1.76 ± 0.689	1.76 ± 0.723	1.72 ± 0.458	0.964

Values are presented as mean±SD, **p* value <0.05 statistically significant

Table 5 Comparison of Cole score in intergroup

Cole score	P versus ML	P versus M	M versus ML
10 min	0.04	0.002	0.14
20 min	0.003	<0.0001	0.0001
30 min	0.001	<0.0001	0.0001
45 min	1	0.509	0.509
1 hour	1	0.09	0.658
2 hours	1	0.81	0.839
Incidence of emergence delirium	0.004	0.02	0.747
Emergence time	<0.001	<0.001	<0.001

* *p* value <0.05 statistically significant

and 5). There was no bronchospasm, laryngospasm, or other complications in all the study groups.

Discussion

Children are more vulnerable to behavioral changes during recovery from anesthesia (Kim et al. 2011; Lapin et al. 1999; Ko et al. 2001). The incidence of postanesthesia agitation is found to be more in children compared to adults. Neurotransmitter level variations such as decreased acetylcholine levels, dopamine, norepinephrine, and aminobutyric acid are seen in neurophysiology in pediatric age groups (Vlajkonic and Sindjelic 2007; Ghai et al. 2015; Nilsson et al. 2008).

One of the critical risk factors for the occurrence of ED has been found to be the use of short-acting inhalational anesthetics where there is a relatively rapid phase of transition between anesthesia and return of consciousness and awareness (Ali and Abdellatif 2013; Tazeroualti et al. 2007). The halogenated inhalational anesthetic agents have been postulated to impair the balance between central neuronal synaptic inhibition and excitation (Lapin et al. 1999 and Ko et al. 2001).

Even though ED usually lasts for a short duration, it is a highly alarming phase that may require supplemental doses of sedatives and analgesics in the PACU (Voepel-Lewis et al. 2003.; Gonsalvez et al. 2018).

Acute stress leads to a series of neuronal responses, which lead to the development of behavioral disorders and anxiety (Viswanath et al. 2015; GuoY et al. 2012). Downregulation of large-conductance calcium-activated potassium channels by acute stress may cause enhanced

N-methyl-D-aspartate (NMDA) receptor activity in the thalamus and amygdala. Thus, the NMDA receptor plays an essential role in the neurobiological mechanisms of emotions such as fear, anxiety, and depression (Nilsson et al. 2008).

Inhalation anesthetics exert transient paradoxical excitatory effects, more so in children. This phenomenon is of major clinical concern, particularly during the emergence of anesthesia. The specific excitation of the locus coeruleus neurons by inhalation anesthetics has been proposed to be one of the etiopathological mechanisms involved in this paradoxical excitation. Another postulation is that the excitation could be the result of GABAergic depolarization/excitation in the neocortical neurons (Lee 2017; ElMmansoury. 2017).

Cole et al. 2002 developed a 5-point scoring scale to assess the postoperative behavior in children, and it has been used in various studies to assess ED.

Studies have demonstrated lower incidences of ED when benzodiazepines were used perioperatively (Sikich and Lerman 2004). In a meta-analysis (Zhang et al. 2013), it was observed that the prophylactic administration of midazolam significantly reduced the incidence of ED in children. In a study by (Cho et al. 2014), it was observed that 0.03 mg/kg of midazolam administered towards the end of surgery reduced ED without a significant delay in emergence time.

In the present study, it was observed that the incidence of ED was less with the use of midazolam compared to propofol. The occurrence of ED in the two midazolam groups was not statistically significant. Patients in the study groups did not have delayed recovery or significant side effects in the postoperative period.

Conclusions

Midazolam in low doses given before extubation is effective in preventing the emergence delirium during the postoperative period in pediatric patients without delay in recovery from general anesthesia.

Limitations of the study

The exact dose of midazolam is not known for the prevention of emergence from general anesthesia. Further similar studies are needed to come to the conclusion regarding the dose required for the prevention of the emergence phenomenon in pediatric patients.

Abbreviations

ED: Emergence delirium; ASA: American Society of Anesthesiologists; Group P: Propofol; Group M: Midazolam; Group ML: Midazolam low dose; HR: Heart rate; MAP: Mean arterial pressure; SpO2: Oxygen saturation; NMDA: *N*-methyl-D-aspartate; PACU: Post-anesthesia care unit.

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None

Authors' contributions

RH has done the study design, literature search, statistical analysis, data interpretation, manuscript preparation drafting, editing, and manuscript review. PSD has worked on literature search, manuscript preparation, statistical analysis, and editing. NK has performed literature search and manuscript preparation. SLK has contributed in editing and manuscript review. GG has performed literature search and manuscript preparation. VP has contributed in editing and manuscript review. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Taken from the Institutional Ethical Committee of BLDEDU's Shri B M Patil Medical College Hospital and Research Centre.
IEC No-EC/313/2018-19.
Written informed consent for participation in the study was taken from the parents/gaurdians.

Consent for publication

Written informed consent was taken from the parents/gaurdians for publication.

Competing interests

The authors declare that they have no competing interests.

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