Original Article

Comparison of bolus dose administration of propofol and dexmedetomidine for incidence of emergence delirium in pediatric patients undergoing surgery with general anesthesia: A randomized, double-blind trial

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Abstract

Background and Aims: Emergence delirium (ED) during the postanesthesia recovery phase presents significant challenges, especially among pediatric patients, with incidence rates spanning from 2% to 80%. This study sought to assess and compare the effectiveness of propofol and dexmedetomidine in addressing ED in pediatric patients undergoing sevoflurane anesthesia. The primary aim was to ascertain the prevalence of ED in both treatment cohorts, while secondary outcomes encompassed postoperative pain, hemodynamic responses, and the occurrence of complications.

Material and Methods: Eighty children aged 2–6 years scheduled for short infraumbilical surgeries under general anesthesia were recruited in this trial. Propofol (1 mg/kg) or dexmedetomidine (0.3 μg/kg) was administered 10 min before completion of surgery. The Paediatric Anaesthesia Emergence Delirium scale was employed to evaluate ED every 5 min following extubation, wherein a score exceeding 12 was indicative of ED. Postoperative sedation was assessed using the Ramsay Sedation Scale, while pain levels were determined through the Face, Legs, Activity, Cry, and Consolability (FLACC) score. Any potential complications were closely monitored.

Results: The incidence of ED at extubation was 2.50% and 70% in group D and P, respectively, and the trend of lower ED incidence was consistently observed at 5, 10, 15, and 30 min postextubation. The relative risk ratio at extubation was 4.103 (95% confidence interval: 2.49–6.76), highlighting a significant reduction of 4.1 times in the risk of ED when dexmedetomidine was administered. The dexmedetomidine group exhibited a lower incidence of postoperative pain.

Conclusion: In comparison to propofol, dexmedetomidine demonstrated superior efficacy in reducing ED and postoperative pain in pediatric patients during general anesthesia, when administered before completion of surgery.

Keywords: Dexmedetomidine, emergence delirium, general anesthesia, pediatric, propofol

Introduction

Emergence delirium (ED) or emergence agitation (EA) is a dissociative state of consciousness that occurs during the recovery from anesthesia, leading to disruptive behaviors.[1] It poses a significant challenge in postoperative care, particularly among the pediatric population. Incidence of ED may range from 2% to 80% in pediatric age group, compared

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to 5%–30% in adult counterparts.[2] This phenomenon is characterized by a complex interplay of factors involving the patient's characteristics, anesthesia administered, the type of surgery performed, and pharmacological influences. Notably, its occurrence is higher among children aged between 2 and 8 years.[1] Clinical manifestations of ED include distressing behaviors such as crying, moaning, and even extreme manifestations like thrashing, kicking, or attempting to leave the operation theater. This behavior not only places the child at risk of physical harm, but also presents challenges for the medical staff in managing the child effectively during this critical phase. This often results in an unpleasant experience for both the child and their caregivers, potentially leading to dissatisfaction with the anesthesia procedure.

Numerous interventions, both pharmacological and nonpharmacological, have been explored in the literature to mitigate the incidence and severity of ED. Among pharmacological options, propofol has been investigated at varying dosages to address this issue.[3,4] However, another promising drug that has garnered attention among pediatric anesthesiologists is dexmedetomidine, which is a selective alpha-2 receptor agonist offering a unique profile of effects, including potent anxiolysis, analgesia, and sedation, all with minimal impact on the respiratory function.[5] Nevertheless, the optimal dosing and timing of administration of dexmedetomidine and propofol remain topics of ongoing investigation.

Considering the aforementioned gap, we designed this study to compare the incidence of ED between two pharmacological interventions, propofol (1 mg/kg) and dexmedetomidine (0.3 μg/kg), in pediatric patients undergoing general anesthesia. We hypothesized that the group receiving dexmedetomidine would exhibit a lower frequency of ED compared to the propofol group. The primary objective of this study was to ascertain the occurrence of ED in both treatment groups. In addition, we explored secondary outcomes, including postoperative pain, hemodynamic parameters, and any other potential complications arising from the intervention.

Material and Methods

After obtaining approval from the institutional ethics committee and registration in the Clinical Trial Registry of India, we enrolled children aged 2–6 years, classified under American Society of Anesthesiologists (ASA) Physical Status (ASA-PS) I and II, who were scheduled for infraumbilical surgeries lasting less than 1 h and requiring general anesthesia. Exclusion criteria comprised children with ongoing upper respiratory tract infections, neurologic disorders, developmental delays, congenital airway abnormalities, cardiac ailments, syndromic conditions, or allergies to the study drugs. The study employed computer-generated random sequence numbers for randomization, utilizing sealed envelopes to ensure allocation concealment. Before the patients were enrolled, comprehensive explanations of the study drugs' potential benefits and adverse effects were provided to parents or caregivers, who then signed the written and informed consent. To ensure double blinding, the observer responsible for assessing the outcome variables remained unaware of the specific study drug that was administered and was different from the one who prepared and administered the study drug.

Children were allocated to two groups, each consisting of 40 participants. All children underwent thorough preanesthetic evaluations and subsequently underwent standardized anesthesia induction. As per the hospital protocol, children were moved to the operating room with an established intravenous (IV) line. All participants were premedicated with midazolam (0.05 mg/kg) before being transferred to the operating room. Standard monitoring equipment including pulse oximetry (SpO_2), five-lead electrocardiogram (ECG), and noninvasive blood pressure (NIBP) were applied, and baseline parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and SpO_2 were recorded.

The induction of anesthesia was achieved using fentanyl (2 μg/kg) and propofol (2–3 mg/kg), with an appropriately sized laryngeal mask airway (LMA) inserted. Subsequently, a caudal block was administered utilizing 0.2% ropivacaine at a dose of 1 ml/kg. Anesthesia was maintained by sevoflurane in a 40% oxygen/air mixture, with spontaneous assisted ventilation. In the intervention groups, children received either propofol (1 mg/kg) for group P or dexmedetomidine (0.3 μg/kg) for group D as a bolus IV injection over 1 min, to be administered 10 min before the completion of surgery. Following completion of the surgical procedure, LMA was removed once the gag reflex was restored, and the children were transferred to the postanesthesia care unit (PACU).

In PACU, the occurrence of ED was assessed at 5-min intervals for a duration of 30 min postsurgery, employing the Paediatric Anaesthesia Emergence Delirium (PAED) scale.[6] An ED label was assigned if the child's PAED score exceeded 12, with severe ED designated if the score exceeded 15. Cases of severe ED were addressed with a propofol rescue bolus (1 mg/kg) administered every 10 min once the potential leading causes of ED had been taken care of.[7] The level of sedation was evaluated every 5 min using the Ramsay sedation scale, and a score exceeding 2 indicated a sedated state.[8] Pain was assessed using the Face, Legs,

Activity, Cry, and Consolability (FLACC) score[9] every 5 min postextubation; fentanyl (1 μg/kg) was administered if the FLACC score surpassed 4. In addition, postoperative sedation and occurrences of bradycardia or hypotension were closely observed and recorded.

Statistical analysis

The sample size was calculated with reference to a previous study[10] that investigated the preventive effects of propofol and dexmedetomidine on sevoflurane-related agitation in pediatric patients undergoing adenotonsillectomy. This earlier study focused on EA just after extubation, where the incidence of ED was reported as 32.5% for the propofol group and 12.5% for the dexmedetomidine group. Calculations were carried out with an alpha error set at 0.05 and a statistical power of 80%. The formula for hypothesis testing concerning two independent sample proportions was employed for sample size estimation. Sample size was calculated to be a minimum of 34 subjects. Considering 10% attrition rate, the derived sample size was determined to be 40 patients for each study group.

The data collected during the study was compiled using a Microsoft Excel spreadsheet and analyzed statistically using the statistical package for the MedCalc statistical software version 19.3 for Window editions. Qualitative data were presented in terms of numbers and percentages, while quantitative data were expressed as mean ± standard deviation (SD) or median, as appropriate. Group comparisons were performed utilizing the χ^2-test, z-test, and unpaired *t*-test, according to the nature of the data. In addition to these, Mann–Whitney U test was used for nonparametric analysis of data if they did not follow a normal distribution. A *P* value of less than 0.05 was considered statistically significant.

Results

A total of 85 subjects who met the inclusion criteria were initially enrolled in the study. However, five children were excluded due to upper respiratory tract infection on the day of surgery. As a result, the final analysis was conducted on 80 subjects, equally divided into two groups denoted as P and D, each comprising 40 participants [Figure 1]. Notably, no significant differences were observed in patient characteristics, including demographic factors like age and gender and recovery profile between the two studied groups [Table 1]. Hemodynamic variables were also comparable between both the groups [Figure 2].

The incidence of ED at extubation was found to be statistically different between the two groups. Specifically, in group P, 28 subjects (70%) experienced ED at extubation, while in group D, only one subject (2.50%) exhibited ED. This trend of lower ED incidence was consistently observed at 5, 10, 15, and 30 min postextubation in group D compared to group P. The calculated relative risk ratio at extubation was 4.103 (95% confidence interval: 2.49–6.76), indicating a substantial reduction of 4.1 times in the risk of ED with dexmedetomidine compared to propofol. The associated *P* value was found to be statistically significant across all time points [Figure 3].

Pain was observed in significantly greater proportion of children in group P compared to group D at various time points postextubation. The relative risk ratio for pain at extubation indicated a value of 2.212 (95% confidence interval: 1.718–2.848), signifying a higher risk of pain with propofol use compared to dexmedetomidine [Table 2].

The median Ramsay sedation scale score at extubation was noted as 2 in group P and 3 in group D, which were statistically nonsignificant. With regard to complications, the occurrence of nausea was reported in two children (5%) in group P, while it was not observed in group D. Pruritus and hypothermia were seen in only one child (2.5%) in group P. Notably, the incidence of complications between the two groups did not show statistically significant differences. There was no significant difference in the length of stay in PACU in both the groups.

Discussion

The principle study findings revealed a significant difference in the incidence of ED between the propofol and dexmedetomidine groups. Specifically, ED was observed in 70% of children receiving propofol, while only 2.5% of children in the dexmedetomidine group exhibited such

Table 1: Demography and recovery time

Parameter	Group P (*n*=40)	Group D (*n*=40)	*P*
Age in years (mean±SD)	3.97±1.67	4.15±1.36	0.596
Gender (M:F)	29/11	28/12	
Recovery time (min)	30.67±4.07	29.3±4.21	0.14

F=Female, M=Male, SD=Standard deviation. Statistical tests used: Chi-square test, Student's t-test

Table 2: Comparison of FLACC scores at various time points

FLACC >4	Group P *n* (%)	Group D *n* (%)	Relative risk	95% CI	*P*
At extubation	7 (17.5%)	0 (0%)	2.212	1.718–2.848	0.011
5 min	7 (17.5%)	1 (2.5%)	2.212	1.718–2.848	0.011
10 min	4 (10%)	0 (0%)	2.111	1.666–2.676	0.115
15 min	2 (5%)	0 (0%)	2.053	1.635–2.578	0.493
30 min	1 (2.5%)	2 (5%)	2.026	1.620–2.533	1.000

CI=Confidence interval, FLACC=Face, Legs, Activity, Cry, and Consolability score. Statistical test used: Student's t-test

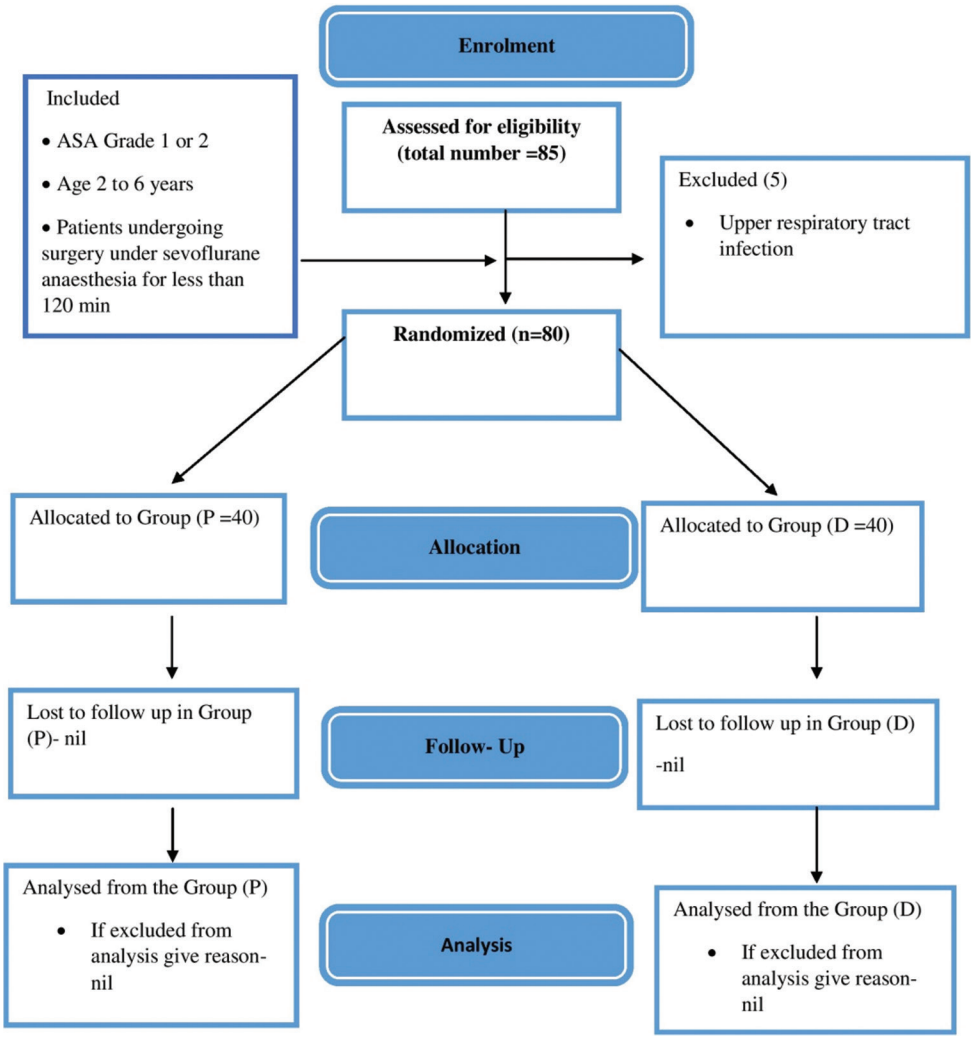

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow chart

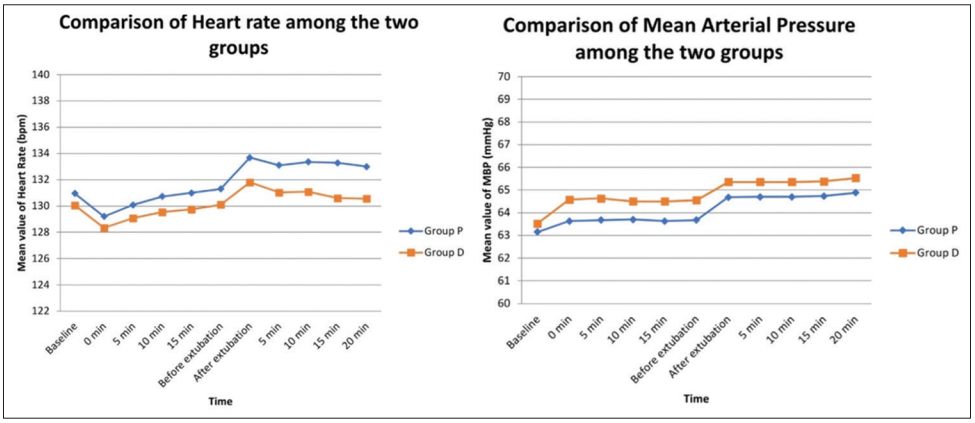

Figure 2: Comparison of mean arterial pressure and heart rate among both the groups. MBP - Mean Blood Pressure

symptoms at extubation. This difference was consistently observed across all measurement time points post-extubation between both the groups. The level of sedation was similar in both the groups, though significantly greater proportion of children experienced pain at emergence in group P.

ED, while often self-limiting, bears significance due to the associated increased morbidity and potential mortality in the pediatric population. It is recognized as a condition with multifactorial origins and is typically diagnosed through exclusion, particularly when no other cause can account for

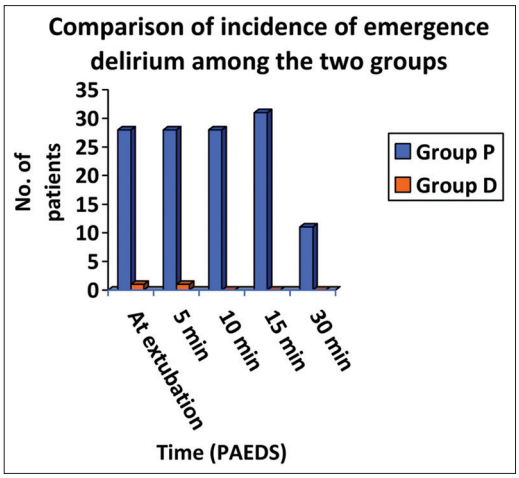

Figure 3: Comparison of ED at various time points. ED = emergence delirium, PAED = Paediatric Anaesthesia Emergence Delirium

the observed abnormal behavioral changes during recovery from general anesthesia. The diagnosis of ED itself presents challenges, given the variety of assessment scales available and the lack of universal consensus on a single validated scale or cut-off value.[6,11,12] In this study, a cut-off value of PAED score greater than 12 was used to identify cases of ED.

Existing studies have delved into the role of both propofol and dexmedetomidine, considering the potential of diverse dosage regimens to prevent ED. Recently, a comprehensive meta-analysis showed the efficacy of a prophylactic propofol dose (3 mg/kg) to effectively curtail the incidence of ED in children undergoing sevoflurane anesthesia, all the while avoiding any undue extension of PACU stay.[3] Another meta-analysis spotlighted the benefits of administering prophylactic propofol (1 mg/kg) before commencement of surgery to be efficacious in prevention of ED.[4] In the realm of dexmedetomidine, a meta-analysis had been done on various dosages and modes of administration (both bolus and infusion) of dexmedetomidine. The findings unveiled the significant efficacy of dexmedetomidine in reducing the occurrence of ED, and the optimal dose of dexmedetomidine was identified to be 0.30 μg/kg (95% confidence interval: 0.21–1 μg/kg). The pooled results of this meta-analysis showed dexmedetomidine to be superior than placebo and midazolam in preventing ED. However, dexmedetomidine was not found to be superior when compared to propofol or ketamine.[5]

Both the drugs have also been compared in various dosage combinations to decrease ED. A study conducted to compare the incidence of ED in dexmedetomidine (0.3 μg/kg) and propofol (1 mg/kg), given 5 min before completion of surgery which was infused over over 5 min, among children undergoing adenotonsillectomy reported less incidence of ED in the dexmedetomidine group.[10] In another study, the incidence of ED was found to be 9.4% and 13.9% in the dexmedetomidine and propofol groups, respectively.[13] In addition, a study conducted by Huang *et al*.[14] comparing the infusion of propofol (2 mg/kg/h) and dexmedetomidine (0.5 μg/kg/h) showed dexmedetomidine to be superior than propofol in reducing the incidence of ED. In contrast, Bong *et al*.[15] did not observe significant benefits from either dexmedetomidine or propofol in reducing the incidence of ED after general anesthesia for magnetic resonance imaging (MRI) studies. However, the administration of drugs in this study was at the time of anesthesia induction. Analgesic and sedative properties of dexmedetomidine contribute to less pain and agitation in children. Propofol lacks analgesic properties, and the sedative action also lasts less than 10 min, so rapid emergence from anesthesia could be a contributing factor of increased incidence of ED compared to dexmedetomidine.[16]

In this study, it is noteworthy that the hemodynamic parameters exhibited stability across both groups, requiring no active interventions. Existing literature has demonstrated varied results, with some studies indicating minimal or no hemodynamic effects upon dexmedetomidine administration, while others have observed a decrease in HR without significant influence on MAP.[10,14,15] This HR reduction attributed to dexmedetomidine's central sympatholytic effect may vary due to factors such as drug concentration, dosage, and mode of administration.

Pain assessment during emergence demonstrated distinct patterns between the two groups. In group P, 17.5% of subjects experienced pain at emergence upon extubation, as indicated by the FLACC scores exceeding 4, while only few children experienced pain in group D. The absence of pain in group D can be attributed to the additional analgesic property of dexmedetomidine. Numerous studies underscore the role of pain as a significant contributing factor to the development of ED.[1,7,17] In various studies, administration of dexmedetomidine in different dosages and routes has consistently shown significant reduction in pain scores.[5,10,14] Importantly, the median Ramsay sedation scores at 30 min postextubation were found to be comparable between both the groups, thus ensuring similar recovery times in them.

The strengths of our study include the utilization of minimal dosages for both dexmedetomidine and propofol, a deliberate approach aimed at mitigating potential adverse effects such as disturbances in hemodynamic parameters. Furthermore, this study focuses on a pivotal demographic group, the pediatric age group of 2–6 years, which is known for heightened susceptibility to separation anxiety and fear. Given these unique characteristics, the significance of identifying and implementing appropriate pharmacological interventions,

along with determination of the minimum effective dosage, is magnified. Along with these aspects, the randomization, clear inclusion criteria, and use of validated tool for assessing ED hold crucial implications for appropriateness of our study results.

Indeed, while this study bears significance, there are certain limitations that warrant acknowledgment. Despite rigorous precautions, some patients within our cohort experienced pain during emergence. This aspect may potentially influence the observed incidence of ED, underscoring the complexity of factors contributing to this phenomenon. Reliance on the PAED scale and the FLACC scale for ED and pain assessment, respectively, introduces subjectivity into our measurements. The absence of a definitive objective diagnostic method for ED poses a challenge in quantifying its occurrence. The absence of preoperative anxiety measurements in our study precludes us from establishing a direct correlation between preoperative anxiety and the incidence of ED, potentially limiting the scope of understanding the broader psychological context. The scope of our follow-up was restricted to 30 min postsurgery. This temporal constraint prevented us from evaluating potential long-term effects of the administered study drugs, which might be pertinent for a comprehensive assessment.

Conclusion

In conclusion, our study contributes valuable insights into the management of ED in the pediatric population undergoing general anesthesia. Notably, dexmedetomidine at a dose of 0.3 μg/kg demonstrated superiority over propofol at 1 mg/kg, when administered just before the end of surgery, in terms of reducing both the incidence and intensity of EA. Furthermore, our study highlights the advantageous analgesic property of dexmedetomidine, and this aspect aligns with the growing recognition of pain as a contributing factor to the development of ED. The stability of hemodynamic parameters, coupled with the comparable levels of sedation and recovery times in both groups, underscores the safety and feasibility of dexmedetomidine and propofol administration.

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Conflicts of interest
There are no conflicts of interest.

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