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**Original Article**

# Premedication Propofol Dose to Prevent Emergency Delirium

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**Abstract**

**Objective:** One of the most common complications in general anesthesia is the Emergence delirium (ED). Many agents have been studied for prevention of ED, among which propofol has been successfully used. However, there is no information about the optimal dosage of this agent considering the ultimate outcome and the adverse effects; therefore, aimed to assess in this study.
**Method:** 70 children undergoing general anesthesia using propofol, fentanyl, and atracurium were assessed. Participants were allocated randomly to treatment with either propofol 1 mg/kg (n = 35) or 0.5 mg/kg (n = 35) by the end of the anesthesia. The Pediatric Anesthesia Emergence Delirium (PAED) Scale, Face, Legs, Activity, Cry, Consolability (FLACC) scale, and the University of Michigan Sedation Scale (UMSS) were assessed by 10-minute intervals. Post-anesthesia care unit (PACU) stay and adverse effects were registered and compared as well.
**Results:** Duration of PACU stay (P < 0.001), PAED (P = 0.001), and UMSS (P = 0.003) were remarkably lower among low-dose propofol-treated children in the assessment at the 30th minute, while there were no significant differences in FLACC scores between the groups (P > 0.05). Apnea was found in a patient (2.85%) treated with high-dose propofol and decreased oxygen saturation was demonstrated in 5 (14.28%) and 2 (5.71%) participants in high- versus low-dose propofol. None of the patients experienced postoperative nausea and vomiting.
**Conclusion:** Based on the current study, propofol 0.5 mg/kg by the end of anesthesia could efficiently prevent ED incidence and reduce time of PACU stay and adverse effects compared to a high dose of 1 mg/kg.

**Key words:** *Anesthesia; Child; Delirium; General; Propofol*

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Emergency delirium (ED) was originally introduced by Eckenhoff *et al.* in 1961 (1). ED is defined as wide ranges of behavioral disturbances, including increased sensitivity to environmental stimuli and exaggerated motor response in the instant post anesthesia presenting as agitation, uncontrollable sobbing, aggression and moaning (2). With an incidence rate of 10-80%, this condition mostly occurs in preschool children 2 to 6-yearsold (3-5).

Variety of risk factors have been reported to associate with ED, among which is age, type of surgery, inadequate pain control, baseline temperament, presence of anxiety before surgery, anesthetic agents and premedication to name a few (6-8).

Anesthetic regimen and premedication drugs are some of the most significant factors related to incidence of ED. Variety of regimens have been proposed for prevention of ED. Ketamine, propofol, alpha-2 agonists, opioids and benzodiazepines have been investigated (5, 9, 10); however, no definite conclusions were made. Keles and colleagues indicated that 3-7 year-old children were premedicated with either dexmedetomidine (2µg/kg) or midazolam (0.5 mg/kg) and presented an appropriate response to both regimens, however, dexmedotimidine was generally superior (11). Ketamine is another agent successfully administered for ED control; however, the best dose to achieve optimal outcome has not been well-elucidated (12, 13).

Propofol is among the agents that have been successfully utilized to prevent ED and is accompanied by promising outcomes compared to sevoflurane-based anesthetic techniques (3). This agent was experimented via bolus injection, slow infusion, and adjunctive infusion. The minimal dosage of 1 mg/kg propofol led to a remarkable decrease in ED incidence (9), while higher doses of 2, 2.5, and 3 mg/kg of this regimen did not affect outcomes (14). The current study's primary principle is to assess and compare the efficacy of 0.5 mg/kg of propofol versus 1 mg/kg of premedication with this agent in prevention and treatment of ED incidence in the post-anesthesia care unit (PACU).

## Materials and Methods

### *Sample*

Seventy children admitted to the Imam Hossein Hospital's Pediatric Surgical Center affiliated with Isfahan University of Medical Sciences, undergoing general anesthesia for any operation from July 2018 to December 2019, were included in this randomized double-blinded controlled trial (RCT).

This study observed all Helsinki declaration rules, and the Ethics Committee at Isfahan University of Medical Sciences confirmed this proposal. Furthermore, this study was approved by the Iranian Registry of Clinical Trials (IRCT20200119046193N1). Study design was simply explained for the patients' legal guardians, and written consent was obtained.

All of the admitted one-to-six-year-old children undergoing general anesthesia general surgery (cleft palate surgery, circumcision, splenectomy, malignancy surgeries, appendicitis, and inguinal or umbilical hernia) and neurosurgeries (craniosynostosis) performed at Imam Hossein Hospital were included. Presence of any psychiatric comorbidity (attention deficit hyperactivity disorder (ADHD), separation anxiety or mood disorders) or central nervous system disease (brain or spine congenital malformations, benign or malignant brain masses, hydrocephalia and requirement for shunt embedding) were defined as the unmet criteria.

Patients were excluded in case the surgical procedure was extended due to any reason that required further anesthetic administration or incidence of any surgically-related complications such as bleeding.

Samples were selected through the convenience method, considering the inclusion requirements. Patients were then randomly divided into two groups of low dose versus high dose treatment with propofol using computerized Random Allocation program where a specific number was assigned randomly to every patient and then was allocated to either interventions.

The patients' legal guardians and the anesthesiologist were not informed about the patient group; guardians were already convinced that medication was randomly administered and they were supposed to be blinded to the type of the regimen, and also, the agents were prepared blindly by another person except for the anesthesiologist and, therefore, he was blinded to the regimen, as well.

### *Measurements*

**Face, Legs, Activity, Cry, Consolability (FALCC) scale:**

FALCC is a scale assessing five separate behavioral patterns induced by pain, including grimacing, motor activity in lower extremity, tearfulness or crying, activity and propensity of being consoled. Each of the entities is rated between 0 and 2, and total pain can be rated between 0 (no pain) and 10 (the most severe pain) (15). Table 1 shows the pattern of scoring in FALCC, which was filled by the physicians.

**The Pediatric Anesthesia Emergence Delirium (PAED) Scale:**

PAED was proposed by Sikich and colleagues in 2004. It embraces five psychometric items scoring from zero to four in terms of severity. These items include 1) the child can keep eye contact, 2) behaviors are targeted, 3) the child considers the environment, 4) the child is agitated, and 5) the child can't be calmed. Items one and three assess disturbances in level of consciousness; item two represents distortions in cognition; items four and five are psychometric tools about disturbances in psychomotor behavior and emotion. Total range of scores is from 0 to 20 (17).

**The University of Michigan Sedation Scale (UMSS):**
UMSS is a 5-point observational scale for assessing sedation depth. Table 2 represents the scoring scale of UMSS (18).

## Intervention and primary outcomes:

All of the studied cases were premedicated using 0.01 mg/kg of midazolam plus 1 mg/kg of ketamine. After achieving deep sleep, the children were separated from their parents and transferred to the operating room for anesthesia induction via 2 mg/kg propofol, 2 mcg/kg fentanyl, and 0.5 mg/kg atracurium. Maintenance was performed by using propofol (200 mcg/kg/min) plus oxygenation by 50% oxygen and 50% air.

By the end of operation and extubation, participants were transmitted to PACU, and the intensity of their pain was assessed every ten minutes using the FLACC scale and in cases with scores over three (19), fentanyl (1 mcg/kg) was used.

The patients' delirium status was evaluated every ten minutes using the Pediatric Anesthesia Emergence Delirium Scale (PAED) (20), and subjects with scores equal or above ten were considered as emergence delirium. Therefore, either low or high doses of propofol were administered.

High dose propofol was defined as 1 mg/kg and the low dose was 0.5 mg/kg for this agent.

Score of sedation was evaluated every ten minutes based on the University of Michigan Sedation Scale (UMSS), and scores ≥ 2 were defined as appropriate sedation.

Modified Aldrete Score was utilized to assess and compare the PACU stay of the two groups (21).

Incidence of complications, including laryngospasm, bronchospasm, decreased oxygen saturation (less than 90%), apnea, nausea, and vomiting, were registered in the checklist.

***Statistical analysis***

Sample size was calculated using the below-mentioned formula where Z1 was 95% confidence interval accounting for 1.96, Z2 was the power of the study considered as 84%, S was the standard deviation of each group and d as the minimal mean difference of the variables equaled 0.7. Eventually, the calculated sample population was 32 per group that increased to 35 by considering a probable 10% risk of loss.

$$n = \frac{(z_1 + z_2)^2 (2s^2)}{d^2}$$

Data were analyzed in SPSS version 25. Descriptive data were reported as absolute numbers, percentages, mean and standard deviation. The Mann-Whitney test, Fisher's exact test, Independent t-test, and Chi-square were used to analyze the information. A p-value of less than 0.05 was determined as level of significance.

**Table 1. Face Leg Activity Cry Consolability (FLACC) Rating for Pediatric Pain**

| Categories | Scoring | | |
|---|---|---|---|
| | 0 | 1 | 2 |
| Face | No specific expression | Occasional frown; uninterested | Frowning quivering chin |
| Leg | Relaxed | Restless | Kicking |
| Activity | Normal position, moving casually | Tense | Rigid posture |
| Cry | Not crying | Moans | Weeping permanently |
| Consolability | Relaxed | Calmed by reassurance | Hard to calm |
| Face (F), Legs (L), Activity (A), Cry (C), Consolability (C) is each rated from 0-2, resulting in score between 0 and 10. | | | |

**Table 2. Detailed Items of the University of Michigan Sedation Scale**

| UMSS score | Description |
|---|---|
| 0 | Alert |
| 1 | Minimally sedated: drowsy with proper answer to sound or calling |
| 2 | Moderately sedated: somnolent, easily aroused with light touch |
| 3 | Deeply sedated: deep sleep arousable solely with significant physical stimulation (e.g. tickling) |
| 4 | Unarousable |

## Results

Eligibility of 100 children undergoing general anesthesia for surgical purposes was evaluated, among which 70 complied with the inclusion requirements and were included. All eligible patients fulfilled the study protocol and were entered into the analysis. Figure 1 is the CONSORT flow-diagram.

Comparing two groups in terms of demographic characteristics including age, gender distribution, and weight revealed insignificant differences. Duration of stay in PACU was remarkably especially among those treated with high doses of propofol ($P < 0.001$). Demographic information is presented in Table 3.

PAED as determinant of delirium was assessed every 10 minutes and compared between the two groups and revealed insignificant difference at baseline (P = 0.942), within 10 (P = 0.363) and 20 minutes (P = 0.087), while the PAED score was remarkably higher among those treated with high doses of propofol (P = 0.001) (Table 4). Repeated measure assessments revealed that the decrease in PEAD scores was statistically significant in both groups (P < 0.05). UMSS assessments were similar in two groups at baseline (P = 0.294). Further assessments in the next 10 (P = 0.109) and 20 minutes (P = 0.436) showed insignificant differences, as well. The two groups were significantly different from the UMSS assessment at the end of the study (P = 0.003). Repeated measure analysis of UMSS showed a statistical decrease in trend of UMSS scores in both treatments of high dose and low dose propofol (P < 0.05). There was no significant statistical difference in FLACC between the two groups (P > 0.05) (Table 4).

Assessment of complications related to the medications showed no laryngospasm, bronchospasm, nausea, and vomiting, whereas apnea occurred in patients treated with high dose propofol (P = 0.186). Besides, seven patients experienced decreased oxygen saturation, among which five patients belonged to the high-dose and two patients belonged to the low-dose propofol therapy (P = 0.001) (Table 5).

**Table 3. Comparison of Demographic Characteristics between High-Dose and Low-Dose-Propofol-Treated Children**

| Variables | | All | Low dose propofol | High dose propofol | P-value |
|---|---|---|---|---|---|
| Age (years), mean ± standard deviation | | 2.6 ± 1.42 | 2.40 ± 1.29 | 2.88 ± 1.54 | 0.978 |
| Gender (N) | Boy | 54 (77.14) | 28 (80) | 26 (74.29) | 0.897 |
| | Girl | 16 (22.86) | 7 (20) | 9 (25.71) | |
| Weight (Kg), mean ± standard deviation | | 12.1 ± 2.8 | 11.9 ± 2.6 | 12.25 ± 3.1 | 0.855 |
| Duration of post-anesthesia care unit stay (minutes), mean ± standard deviation | | 37.4 ± 7.5 | 34.28 ± 6.5 | 40.5 ± 7.2 | < 0.001 |

**Table 4. Comparison of Delirium Score, Sedation Status, and Pain Intensity between Low Dose and High Dose Propofol Treated Children**

| Variables | All | Low dose propofol (N = 35) | High dose propofol (N = 35) | P-value |
|---|---|---|---|---|
| | | The Pediatric Anesthesia Emergence Delirium Scale | | |
| Baseline | 7.8 ± 2.3 | 7.9 ± 1.76 | 7.65 ± 2.82 | 0.942 |
| Within 10 minutes | 7.7 ± 2.2 | 7.7 ± 2.19 | 7.65 ± 2.38 | 0.363 |
| Within 20 minutes | 6.7 ± 1.6 | 6.54 ± 1.22 | 6.94 ± 1.95 | 0.087 |
| Within 30 minutes | 6.2 ± 0.98 | 6.08 ± 0.74 | 6.37 ± 1.16 | 0.001 |
| P-value | | 0.156 | 0.187 | |
| | | The University of Michigan Sedation Scale | | |
| Baseline | 1.24 ± 0.76 | 1.31 ± 0.71 | 1.17 ± 0.82 | 0.294 |
| Within 10 minutes | 0.9 ± 0.64 | 0.77 ± 0.54 | 1.02 ± 0.70 | 0.109 |
| Within 20 minutes | 0.7 ± 0.79 | 0.65 ± 0.72 | 0.82 ± 0.85 | 0.436 |
| Within 30 minutes | 0.48 ± 0.77 | 0.2 ± 0.42 | 0.77 ± 0.91 | 0.003 |
| P-value | | 0.298 | 0.254 | |
| | | Face, Legs, Activity, Cry, Consolability scale. | | |
| Baseline | 1.97 ± 0.53 | 1.94 ± 0.41 | 2 ± 0.64 | 0.820 |
| Within 10 minutes | 1.6 ± 1.97 | 1.6 ± 0.6 | 1.6 ± 0.69 | 0.838 |
| Within 20 minutes | 1.11 ± 0.57 | 1.11 ± 0.58 | 1.11 ± 0.58 | 1.00 |
| Within 30 minutes | 0.857 ± 0.54 | 0.85 ± 0.6 | 0.85 ± 0.49 | 0.934 |
| P-value** | | 0.844 | 0.985 | |

**Table 5. Complications Associated with Low Dose versus High Dose Propofol Treatment**

| Complications | All | Low-dose propofol N (%) | High-dose propofol | P-value |
|---|---|---|---|---|
| Bronchospasm | 0 (0) | 0 (0) | 0 (0) | |
| Laryngospasm | 0 (0) | 0 (0) | 0 (0) | |
| Decreased oxygen saturation | 7 (10) | 2 (5.71) | 5 (14.28) | 0.001 |
| Apnea | 1 (1.42) | 0 (0) | 1 (2.85) | 0.186 |
| Nausea and vomiting | 0 (0) | 0 (0) | 0 (0) | |

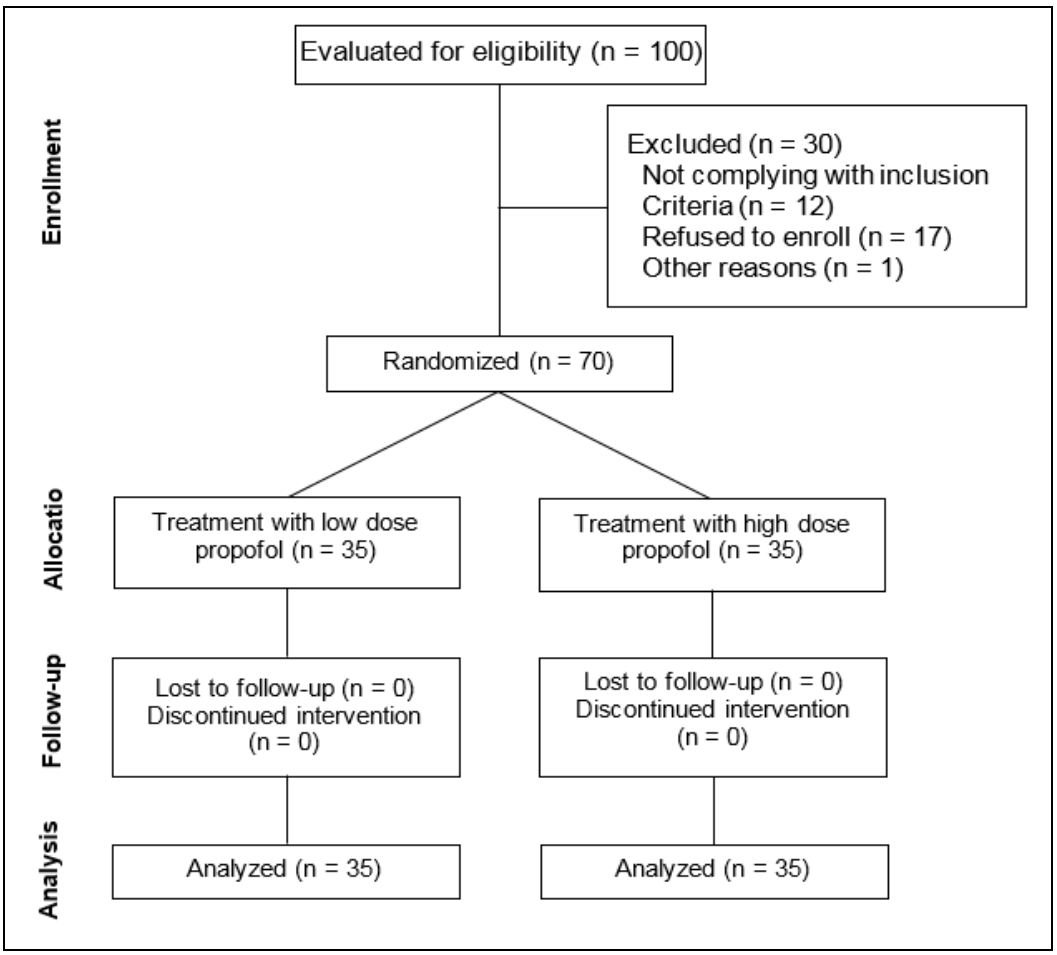


**Figure 1. CONSORT Flow-Diagram of the Clinical Trial**

## Discussion

In the current study, we observed that the use of 0.5 mg/kg propofol could efficiently prevent ED incidence as none of the treated patients with this dose presented ED based on the PAED. Besides, we achieved acceptable sedation status and pain intensity within 30 minutes of stay in PACU. Other aspects representing superiority of low-dose propofol to its high dose (1 mg/kg) included better scores of PAED, pain intensity, sedation, and less adverse effects limited only to a decrease in oxygen saturation in 5.71% of patients and requirement of shorter stay in PACU.

Incidence of ED and its prevention in children undergoing general anesthesia has been a matter of debate for many years. Numerous medications have been proposed to prevent and treat this condition with diverse outcomes (3, 22). In general, literature has shown promising data regarding the use of propofol for prevention of ED; however, the best dose with minimal adverse effects has not been well documented.

Kim *et al.* conducted a study on 101 children undergoing general anesthesia using sevoflurane for strabismus surgery. To prevent ED, three medications including 1 mg/kg propofol, 0.5 mg/kg midazolam, and saline as the control, were administered. In agreement with our findings, they found a remarkably lower rate of ED incidence among the propofol-treated patients than saline-treated ones; however, there was no difference between midazolam and propofol. A surprising finding of their study was elongated ED among those treated with propofol or midazolam than the control group. The least adverse effects were found among propofol-treated children (23).

Kim and colleagues performed another study on children less than six years old to assess the efficacy of 1 mg/kg propofol versus 1 mg/kg of fentanyl and saline as control. They found the least incidence of ED, the least scores of PAED, and the least incidence of post-anesthesia nausea and vomiting among propofol-treated patients; however, use of propofol could not effectively reduce stay in PACU (24).

Ali and colleagues conducted a study in order to assess the preventive efficacy of 1 mg/kg of propofol with 0.3 ug/kg dexmedetomidine and saline as the control on ED incidence and, in line with previous studies, demonstrated significant superiority of propofol at this dose in terms of ED incidence, PAED score, pain intensity, duration of PACU stay and time of emergence among those who had experienced ED. Nevertheless, the groups were not remarkably different in terms of nausea and vomiting incidence (25).

A surprising finding presented by Bong *et al.* on children under general anesthesia for magnetic resonance imaging revealed an insignificant difference between 1 mg/kg propofol with 0.3 ug/kg dexmedetomidine or saline in incidence and severity of ED as well as incidence of adverse effects (26). These results were presented by Lee *et al.*, who assessed the premedication of 1 mg/kg propofol versus saline in incidence of ED among 3-8-year-old children undergoing adenotonsillectomy where there was significant reduction in the incidence of ED in both groups, but there was no significant difference in the duration of ED between the two groups. Other similarities found between the two groups included duration of PACU stay, duration of extubation, and postoperative nausea and vomiting (27).

Combination of propofol with ketamine was superior to mere administration of propofol in ED prevention and recovery time period among children undergoing tonsillectomy but did not reach significance (28). Contrary to most studies mentioned above that preferred propofol use, Mahdavi Rad and colleagues presented similar beneficial outcomes for either propofol or midazolam use near the end of tonsillectomy after Isoflurane anesthesia (29). The other study opposing propofol use presented that 0.3 μg/kg dexmetomidine could better prevent ED than 1 mg/kg propofol; however, dexmetomidine caused a significantly deeper and more elongated sedation (20).

Nevertheless, most of the previous studies have presented data in favor of premedication with propofol for prevention of ED at end of anesthesia due to the short half-life of this agent; according to our most recent search, there is no previous study to assess different doses of propofol in order to obtain the best ED preventive outcomes with the least adverse effects. Only two studies in the literature assessed different doses of propofol for ED prevention; however, they evaluated this efficacy in induction but not for the end of stage of anesthesia. The first study by Vitenan in 1999 assessed 3 mg/kg propofol (30) and a study by Bal, *et al.* assessed 2-2.5 mg/kg propofol (31). None of the studies revealed promising data that may have occurred due to a short duration of propofol action, which leads to low serum levels of this agent to play a role in agitation control after surgery.

In summary, according to current research, the present study is among the first to evaluate use of 0.5 mg/kg propofol in ED prevention following general anesthesia in preschool-aged children and found promising outcomes. Besides, comparison of this dose with of the 1 mg/kg dose used routinely for ED prevention showed promising superior outcomes of the low dose in controlling pain intensity, duration of PACU stay, adverse effects, and sedation status.

## Limitation

A significant limitation of our study was not controlling for the probable confounding variables that could affect outcomes such as type of surgery, as it seems that ED and its severity was more prominent among those undergoing head and neck surgery. Most studies in the literature have evaluated the use of propofol among those undergoing sevoflurane anesthesia, an agent which is most popular for incidence of ED, but our patients underwent anesthesia induction by propofol, atracurium, and fentanyl.

## Conclusion

Based on the current study, low dose propofol administration by the end stage of the general anesthesia could efficiently prevent ED incidence. Moreover, comparison of low versus high dose of this agent successfully led to shorter PACU stay and had fewer drug-related complications. Further investigations to generalize the data are strongly recommended.

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## Conflict of Interest

The authors declare no conflicts of interest.

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