

A Single Dose of Propofol at the End of Surgery for the Prevention of Emergence Agitation in Children Undergoing Strabismus Surgery during Sevoflurane Anesthesia

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Background: Emergence agitation in children after sevoflurane is common. Different drugs have been used to decrease its occurrence with variable efficacy. The authors compared the incidence and severity of emergence agitation in children who received a single dose of propofol at the end of strabismus surgery versus children who received saline.

Methods: In this prospective, randomized, double-blind study, the authors enrolled 80 healthy children aged 2–6 yr. The children were randomly allocated to the propofol group (n = 41), which received 1 mg/kg propofol at the end of surgery, or to the saline group (n = 39), which received saline.

Results: The mean scores on the Pediatric Anesthesia Emergence Delirium scale were significantly lower in the propofol group compared with the saline group (8.6 ± 3.9 vs. 11.5 ± 4.5 ; $P = 0.004$). Also, the incidence of agitation was significantly lower in the propofol group compared with the saline group (19.5% vs. 47.2%; $P = 0.01$). A threshold score greater than 10 on the Pediatric Anesthesia Emergence Delirium scale was the best discriminator between presence and absence of emergence agitation. Times to removal of the laryngeal mask airway (10.6 ± 1.5 vs. 9.4 ± 1.9 min; $P = 0.004$) and emergence times (23.4 ± 5.7 vs. 19.7 ± 5 min; $P = 0.004$) were significantly longer in the propofol group. However, discharge times were similar between the two groups (propofol: 34.1 ± 8.4 min; saline: 34.9 ± 8.6 min). More parents in the propofol group were satisfied.

Conclusions: In children undergoing strabismus surgery, 1 mg/kg propofol at the end of surgery after discontinuation of sevoflurane decreases the incidence of agitation and improves parents' satisfaction without delaying discharge from the postanesthesia care unit.

THE occurrence of emergence agitation in children after sevoflurane anesthesia is common, with an incidence ranging between 10% and 80%.^{1,2} Different drugs such as nonopioid analgesics,^{3,4} opioids,⁵ benzodiazepines,⁶ intravenous anesthetics,⁷ and α_2 agonists^{2,8-10} have been used with variable success to allow a smooth emergence from sevoflurane anesthesia. Also, a wide variety of measurement tools have been used to assess this postanesthesia

phenomenon, which makes comparisons of the results between studies difficult.

It is well known that avoiding sevoflurane and using propofol-based anesthetics is associated with a smoother recovery profile.^{11,12} However, despite the fact that propofol-based anesthesia allows for a smoother recovery as compared with sevoflurane in children, maintenance with sevoflurane remains a common practice in many institutions. Among all inhalational anesthetics, sevoflurane is considered the agent of choice for induction and maintenance of anesthesia in children and enjoys wide acceptance among pediatric anesthesiologists. Our hypothesis is that in children receiving sevoflurane for induction and maintenance of anesthesia, the administration of a single dose of propofol just at discontinuation of sevoflurane would decrease the incidence of emergence agitation without delaying emergence from anesthesia or discharge from the postanesthesia care unit (PACU).

We designed this prospective, randomized, double-blind study to test this hypothesis. We compared the incidence and severity of emergence agitation as well as the emergence and discharge times in a group of children receiving a single dose of propofol at the end of surgery after discontinuation of sevoflurane versus a second group of children receiving saline.

Materials and Methods

After institutional review board (American University of Beirut, Beirut, Lebanon) approval and written informed consent from parents, 80 healthy children aged 2–6 yr, with American Society of Anesthesiologists physical status I or II, scheduled to undergo strabismus surgery during general anesthesia were prospectively enrolled in the study and randomly assigned by means of random numbers generated by a computer to either a propofol group or a saline group. Exclusion criteria included mental disease, neurologic disease, treatment with sedatives, full stomach, or indication for rapid sequence induction.

Children fasted for 8 h and received 0.5 mg/kg oral midazolam 15–30 min before separation from the parents. The number of children who were agitated or combative during induction of anesthesia despite premedication with midazolam was recorded in each group. An electrocardiogram, pulse oximeter, noninvasive arterial blood pressure monitor, and rectal temperature probe were attached, and an inhalational induction was

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performed with sevoflurane. After achieving adequate depth of anesthesia, as evidenced by the need and tolerance of an oral airway, an intravenous line was inserted on the dorsum of the hand, and 1 mg/kg intravenous lidocaine was injected, after which breathing was gently assisted for approximately 90 s before the insertion of a flexible laryngeal mask airway (LMA) (*LMA-Flexible™*; The Laryngeal Mask Company Limited, Oxon, United Kingdom) *via* which all children received controlled ventilation to maintain an end-tidal carbon dioxide between 35 and 40 mmHg. After induction of anesthesia, all patients received 15 mg/kg intravenous paracetamol (Perfalgan; UPSA Laboratories, Agen, France) for the control of postoperative pain and 1 mg/kg intravenous dexamethasone (maximum 16 mg) for the control of postoperative pain,¹³ nausea, and vomiting. Anesthesia was maintained with 60% nitrous oxide in oxygen, supplemented by an end-tidal concentration of 2–3% sevoflurane. At the completion of surgery, all children received eye ointment in both eyes without an eye patch. Sevoflurane and nitrous oxide were discontinued, and patients in the propofol group ($n = 41$) received 1 mg/kg propofol, whereas patients in the saline group ($n = 39$) received the same volume of saline. Propofol or saline were administered by the resident according to the group to which the patient was randomized. The anesthesiologist collecting the data was blinded to the group to which the patient was assigned. The LMA was removed whenever the child resumed adequate spontaneous breathing after separation from controlled ventilation. After removal of the LMA, the child was transferred to the PACU. Upon arrival to the PACU, all children were received by one of their parents, who stayed with them until discharge. The Pediatric Anesthesia Emergence Delirium (PAED) scale devised by Sikich *et al.*¹⁴ (table 1) was used to assess emergence agitation. Also, emergence agitation was graded on a four-point scale: 1 = calm; 2 = not calm but could be easily consoled; 3 = moderately agitated or restless and not easily calmed; 4 = combative, excited, or disoriented, thrashing around.¹⁵ This score was used to calculate the incidence of agitation, where agitation scores of 1 and 2 were regarded to represent nonproblematic behavior

and were analyzed as absence of agitation, and scores of 3 and 4 were regarded to indicate agitation and were analyzed as presence of agitation. Values of the PAED scale and the four-point scale were obtained each by a different investigator in all children; the anesthesiologist assessed agitation using the PAED scale and the PACU nurse using the four-point scale. Agitation was assessed immediately after removal of the LMA, and continuously thereafter until all children were calm. The highest scores were recorded. In the PACU, the nurse and the anesthesiologist who recorded measurements and observations were unaware of the group to which the child was assigned. Also, parents and patients were blinded to the treatment allocation. The following time intervals were recorded: duration of surgery, duration of sevoflurane administration (from the start of induction till discontinuation of sevoflurane), and duration of anesthesia (from the start of induction till removal of LMA). Also, the following time intervals were recorded from the time of discontinuation of sevoflurane: the time to removal of LMA; the time to the first response to a simple verbal command, which is defined as time of emergence; and the onset and duration of agitation whenever it occurred. Children's pain was evaluated in the PACU by questioning and observing the behavior using a numerical rating scale at 5, 10, and 30 min after emergence, where 0 corresponds to "no pain," 1 to "slight pain," 2 to "moderate pain," 3 to "severe pain," and 4 to "the worst imaginable pain."¹⁶ Intravenous morphine, 0.1 mg/kg, was administered to treat agitation upon parents' request or to treat pain whenever pain scores were greater than 2. Heart rate and blood pressure, as well as the incidence of adverse events such as vomiting, laryngospasm, and oxygen desaturation, were noted. Children were discharged from the PACU when hemodynamically stable, fully awake, and free of pain, vomiting, or agitation. Immediately before discharge, parents were asked to assess the quality of the PACU stay of their children based on the following satisfaction scale: 1 = excellent, 2 = good, 3 = poor, 4 = bad.

Statistical Analysis

This study was powered on the basis of preliminary results showing 50% incidence of emergence agitation in the control group. A sample size of 32 in each group was calculated to detect a decrease in the incidence of agitation down to 15% with $\alpha = 0.05$ and $\beta = 0.2$. Continuous data were reported as mean \pm SD and were analyzed using an independent sample *t* test, or analysis of variance for multiple comparisons with least significant difference test for *post hoc* analysis. Categorical data were reported as percentages and were analyzed using the chi-square test or Fisher exact test as appropriate. Nonparametric data such as pain scores were reported as median and interquartile range and were analyzed using the Mann-Whitney U test. A *P* value less than 0.05 was considered statis-

Table 1. The Pediatric Anesthesia Emergence Delirium Scale Devised by Sikich *et al.*¹⁴

1. The child makes eye contact with the caregiver
2. The child's actions are purposeful
3. The child is aware of his or her surroundings
4. The child is restless
5. The child is inconsolable

Items 1, 2, and 3 are reversed scored as follows: 4 = not at all, 3 = just a little, 2 = quite a bit, 1 = very much, 0 = extremely. Items 4 and 5 are scored as follows: 0 = not at all, 1 = just a little, 2 = quite a bit, 3 = very much, 4 = extremely. The scores of each item were summed to obtain a total Pediatric Anesthesia Emergence Delirium score. The degree of emergence delirium increased directly with the total score.

Table 2. Patient Characteristics and Durations of Anesthesia and Surgery

	Propofol Group (n = 41)	Saline Group (n = 36)
Age, yr	4.2 ± 1.4	4.3 ± 1.3
Weight, kg	19.2 ± 4.8	18.1 ± 4.6
Sex, M/F	46/54	58/42
Children undergoing repeat surgery	19.5	11.2
Eyes operated, one eye/two eyes	44/56	56/44
Incidence of preoperative agitation	9.7	5.5
Duration of surgery, min	14.1 ± 4.8	16.1 ± 5.8
Duration of anesthesia, min	37.8 ± 6.2	39.9 ± 7.1
Duration of sevoflurane administration, min	27.6 ± 6	30.4 ± 6.8

Values are mean ± SD, or percent. No statistical significance between the two groups.

tically significant. The sensitivity of the PAED scale was investigated using receiver operating characteristic curve methodology¹⁷; the PAED scale scores were correlated with the dichotomous outcome of presence or absence of emergence agitation as per the four-point scale.

Results

Eighty children were enrolled in the study protocol (n = 41 in the propofol group and n = 39 in the saline group). Three patients were excluded from the saline group because of incomplete data collection. Therefore, 41 patients in the propofol group and 36 patients in the saline group were analyzed.

Patient characteristics, as well as the different durations of anesthesia and surgery, were not statistically significant between the two groups (table 2).

The mean scores of the PAED scale and the incidence of emergence agitation were significantly lower in the propofol group as compared with the saline group ($P = 0.004$ and $P = 0.01$, respectively; table 3).

Of the 77 children analyzed, 25 children developed emergence agitation (fig. 1). The mean scores of the PAED scale of those children emerging with agitation was 15.1 ± 3.4 , versus 7.4 ± 2.1 in the 52 children who

were not agitated ($P < 0.001$). A threshold score of the PAED scale greater than 10 was the best discriminator between presence and absence of agitation after emergence from anesthesia (fig. 1). The area under the receiver operating characteristic curve for the PAED scale score greater than 10 was 0.98 (fig. 2), with a true-positive rate (sensitivity) of 0.88 and a false-positive rate (1-specificity) of 0.039. We also calculated the PAED scale scores of the children who had unilateral strabismus surgery versus children who had bilateral strabismus surgery; when treatment groups were examined separately, there was no significant effect of bilateral surgery in the propofol group. There was, however, a significant effect of bilateral surgery on the incidence of agitation in the saline group (table 4).

The time to removal of the LMA and the emergence time were significantly longer in the propofol group as compared with the saline group ($P = 0.004$; table 3). The onset and duration of agitation in those children who were agitated were comparable between the two groups (table 3). All agitation episodes were self-limited. Although 0.1 mg/kg morphine was offered to children with prolonged agitation, all parents elected to avoid pharmacologic interventions and to console their children on their own. As such, none of the patients received morphine. The median of the highest pain scores recorded postoperatively was 1 (1-2) in the propofol group and 1 (1-2) in the saline group ($P = 0.5$). No children required additional analgesics. More parents in the propofol group rated the quality of the PACU stay of their children as excellent as compared with the saline group ($P = 0.002$; table 3). No adverse events such as laryngospasm, oxygen desaturation, or vomiting episodes were recorded during the study period. Children in both groups had similar discharge times from the PACU (table 3).

Discussion

Numerous clinical studies have shown that emergence agitation in children is a common phenomenon after

Table 3. Characteristics of the Emergence Phase and the Recovery Phase in the Postanesthesia Care Unit

	Propofol Group (n = 41)	Saline Group (n = 36)	P Value
PAED scale score	8.6 ± 3.9	11.5 ± 4.5	0.004
Incidence of agitation	19.5	47.2	0.01
Time to removal of LMA, min	10.6 ± 1.5	9.4 ± 1.9	0.004
Emergence time, min	23.4 ± 5.7	19.7 ± 5	0.004
Onset of agitation, min*	24.4 ± 6.8	20.7 ± 6	0.18
Duration of agitation, min*	17.5 ± 6.5	15.3 ± 5.4	0.38
Parents rating satisfaction excellent	75.6	41.7	0.002
Duration of PACU stay, min	34.1 ± 8.4	34.9 ± 8.6	0.68

Values are mean ± SD, or percent. P values less than 0.05 are considered significant.

* The analysis of those two parameters includes the number of children who were agitated after emergence from anesthesia (n = 8 in the propofol group and n = 17 in the saline group).

LMA = laryngeal mask airway; PACU = postanesthesia care unit; PAED = Pediatric Anesthesia Emergence Delirium.

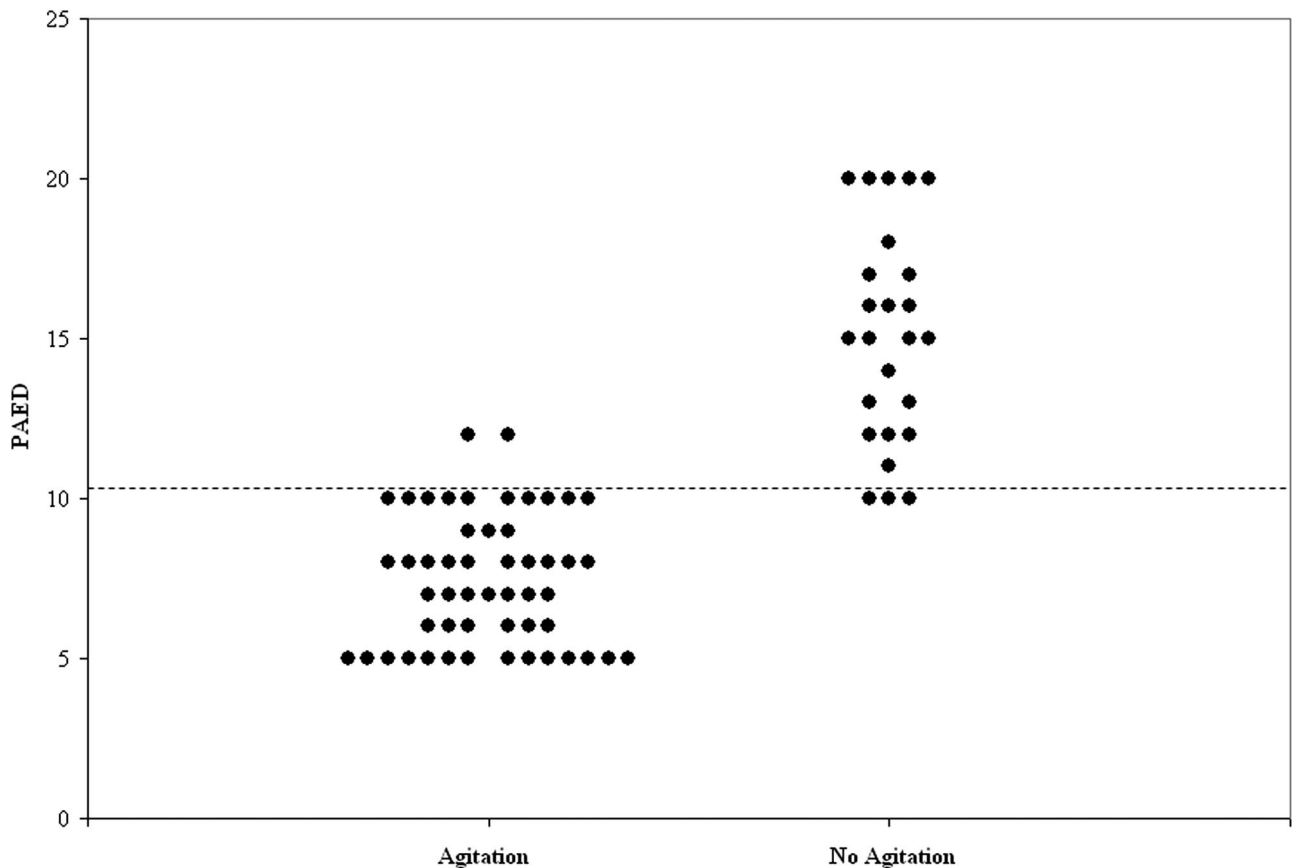


Fig. 1. Comparison of “no agitation” and “agitation” after emergence from anesthesia based on the Pediatric Anesthesia Emergence Delirium (PAED) scale scores, where agitation refers to a score of 3 or 4 on the four-point scale. A threshold score of the PAED scale greater than 10 was the best discriminator between presence and absence of agitation after emergence from anesthesia.

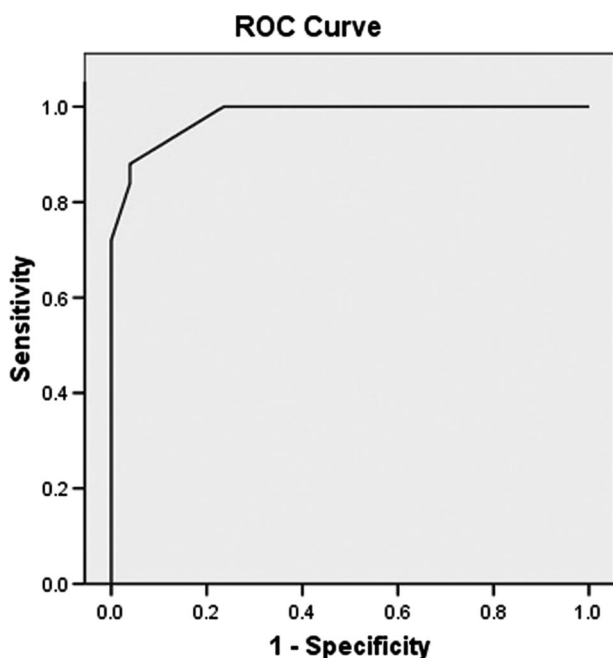


Fig. 2. Receiver operating characteristic (ROC) curve for the sensitivity (true positive) and 1-specificity (false positive) for scores on the Pediatric Anesthesia Emergence Delirium scale. For a score greater than 10, a sensitivity of 0.88 and a 1-specificity of 0.039 were found.

sevoflurane or desflurane-based anesthetics, with an incidence that is significantly higher compared with halothane or propofol-based anesthetics.^{1,3,11,12,18-20} Three previous studies have shown that the incidence of emergence agitation after propofol maintenance of anesthesia ranges from 0-9%, as compared with a range of 23-46% after sevoflurane maintenance.^{11,12,21} In an attempt to minimize emergence agitation after desflurane, Cohen *et al.*²² supplemented the inhalational anesthetic with 2 mg/kg propofol at the beginning of surgery. However, the authors did not demonstrate any reduction in the incidence of emergence agitation.²² This result is expected because propofol has a short duration of action that may not outlast the duration of the surgery. We investigated the effect of 1 mg/kg propofol administered after discontinuation of sevoflurane at the end of surgery and found that the PAED scale scores, as well as the incidence of emergence agitation, were significantly decreased in the propofol group compared with the saline group, and parental satisfaction was significantly improved. Therefore, the timing of short-acting interventions toward the end of surgery, such as a propofol bolus, would seem to be an important factor to emphasize.

In our study, the average PAED scale score was 8.6 ± 3.9 in the propofol group *versus* 11.5 ± 4.5 in the saline

Table 4. Characteristics of the Emergence Phase and the Recovery Phase in the Postanesthesia Care Unit in Children Undergoing Surgery in One Eye versus Two Eyes

	Propofol Group		Saline Group		P Value
	One Eye (n = 18)	Two Eyes (n = 23)	One Eye (n = 20)	Two Eyes (n = 16)	
PAED scale score	8.3 ± 2.7	8.9 ± 4.7	10 ± 4	13.2 ± 4.5	0.003

Values are mean ± SD. Analysis of variance was used. *P* values less than 0.05 are considered significant.

Post hoc analysis with least significant difference test: *P* = 0.001 between propofol group–one eye and saline group–two eyes; *P* = 0.002 between propofol group–two eyes and saline group–two eyes; *P* = 0.023 between saline group–one eye and saline group–two eyes.

PAED = Pediatric Anesthesia Emergence Delirium.

group (*P* = 0.004). Whenever a statistically significant difference is found in a health status measure, it is useful to determine whether this difference is clinically relevant. Effect size, which is the mean change of the variable divided by the SD of that variable, is used to interpret changes in health status.^{23,24} The effect size in our study was 0.72, which is a large health status change. Therefore, the statistically significant reduction in the PAED scale scores observed in our study is clinically relevant.

The PAED scale proposed by Sikich *et al.*¹⁴ is a reliable and valid tool that may minimize measurement error in the clinical evaluation of emergence agitation. However, the calculation of the incidence of agitation with this scale is not possible. Sikich *et al.*¹⁴ identified a threshold value of 10, above which treatment of emergence agitation is required. Similarly, we identified a threshold value greater than 10 to discriminate between the presence and absence of emergence agitation.

Ophthalmology procedures in children may be associated with a high incidence of emergence agitation that may be related to visual disturbances.²⁵ Przybylo *et al.*²⁵ found that 44% of children have altered behavior on emergence from anesthesia after strabismus surgery. This is comparable to the incidence of emergence agitation that we found in the control group in our study. In addition, when we compared the incidence and severity of agitation in children undergoing surgery in two eyes versus one eye in both groups, we were able to identify surgery in both eyes as being associated with an increased incidence of emergence agitation only in the saline group. In the treatment group, the administration of propofol may have neutralized the negative effect of bilateral surgery on emergence agitation.

A limitation to the use of the PAED scale score in the assessment of emergence agitation after strabismus surgery is the presence of the item regarding eye contact. Although none of our children had their eyes patched after surgery, the presence of eye ointment may interfere with the ability of the child to make eye contact with the caregiver, which may be misinterpreted as high scores on item 1. However, the anesthesiologist recording the scores did not mention having much difficulty in the assessment of this item of the PAED scale score.

The improved recovery profile in the propofol group was associated with a significantly longer mean time to removal of LMA (approximately 1 min) and emergence from anesthesia (approximately 4 min) compared with the saline group. This is consistent with previous studies showing that the time to awakening correlates negatively with emergence agitation scores.^{14,26} However, this statistically significant difference is of small magnitude and is not clinically significant. Moreover, the delayed removal of LMA and emergence from anesthesia did not delay discharge; children in both groups had comparable durations of PACU stay.

Despite the fact that strabismus surgery is well known to cause a high incidence of postoperative nausea and vomiting,²⁷ none of our children vomited in the PACU. This finding may be explained by the following facts: Only paracetamol, a nonopioid analgesic was administered, in addition to dexamethasone that possesses both analgesic¹³ and antiemetic properties. No morphine was administered to any of the children. Also, children stayed for approximately half an hour in the PACU. Discharge from the PACU coincided with the end of the study period. Therefore, the occurrence of delayed nausea and/or vomiting may have not been recorded by the investigators.

In conclusion, the administration of a single dose of 1 mg/kg propofol after discontinuation of sevoflurane at the end of surgery in children undergoing strabismus surgery decreases significantly the incidence of agitation and improves parental satisfaction without delaying discharge from the PACU.

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