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Induction with Propofol Decreases Emergence Agitation in Pediatric Patients

Onur Koyuncu[1*], Mustafa Ozgur[2], Cagla Akkurt[3], Selim Turhanoglu[3], Bulent Akcora[4], Mehmet Emin Celikkaya[4] and Alparslan Turan[5]

[1]*Department of Anesthesiology and Department of Outcomes Research, Mustafa Kemal University Tayfur Ata Sokmen Medicine Faculty, Hatay, Turkey*

[2]*Department of Anesthesiology, Antakya Devlet Hastanesi, Hatay, Turkey*

[3]*Department of Anesthesiology, Mustafa Kemal University Tayfur Ata Sokmen Medicine Faculty, Hatay, Turkey*

[4]*Department of Pediatric Surgery, Mustafa Kemal University Tayfur Ata Sokmen Medicine Faculty, Hatay, Turkey*

[5]*Department of Outcomes Research, Cleveland Clinic, Cleveland, USA*

[*]**Corresponding author:** Onur Koyuncu, Department of Anesthesiology, Mustafa Kemal University, Tayfur Ata Sokmen Medicine Faculty, Serinyol, Hatay, Turkey, Tel: 90-326-2291000; E-mail: onurko@yahoo.com

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Abstract

Background and objectives: Emergence agitation (EA) is a common complication seen after inhalational anesthesia especially with sevoflurane, with an incidence of 20-80%. The hypothesis of the study was that induction with propofol reduces the incidence and severity of emergence agitation when compared with sevoflurane in children undergoing inguinal hernia surgery.

Methods: 116 Children undergoing inguinal hernia were randomly assigned to two groups: Sevoflurane group received sevoflurane increasing concentrations up to 8% and propofol group received 3 mg kg propofol in induction. Postoperative agitation treatment and analgesia was standardized, and postoperative assessments included Cole Agitation Scale and narcotic consumption for agitation, Wong-Baker Faces Pain Rating Scale for pain, first spontaneous eye opening time, first verbal command follow time, post-anesthesia care unit (PACU) staying time, first analgesic requirement time and parents satisfaction.

Results: The incidence of EA at arrival in PACU and the cumulative incidences at the end of the postoperative two hours were significantly lower in the propofol group. EA scores were lower in propofol group in all measurement times during postoperative 30 minutes. Fentanyl consumption at arrival in PACU and the sum of the two hours were significantly lower in propofol group. Pain scores were lower in propofol group in the postoperative 24 hours. First analgesic requirement time and parents satisfaction were higher in propofol group.

Conclusion: Propofol in accurate dose is effective in reducing the incidence and intense of EA in children undergoing inguinal hernia and maybe preferred in children with high risk of EA.

Keywords: General anesthesia; Sevoflurane; Propofol; Emergence agitation; Children

Background

Currently more than 400000 pediatric patients are admitted for surgery only in United States annually [1]. Recoveries from these surgeries are sometimes complicated with adverse events. Emergence agitation (EA) is one of the most common and terrifying complication seen after inhalational anesthesia, with an estimated incidence of 20–80% [2,3].

Emergence agitation is described as non-purposeful restlessness and agitation, thrashing, crying or moaning, involuntary physical activities, disorientation, and incoherence after extubation [4]. Patients can even harm themselves by disrupting surgical site, and dislocate indwelling catheters [5]. Mechanisms behind EA are still not clear. Suggested mechanisms involve variable rate of recovery of certain brain areas like late emergence of cognitive function when compared with other areas (such as locomotion and audition) causes the confusion state [6], and various animal and human studies demonstrated that sevoflurane exerts transient paradoxical excitatory effects by exciting neurons in the locus coeruleus [7]. Rapid emergence from anesthesia has also been suspected as a risk factor [8].

Various pharmacological agents have been used to reduce the incidence of EA, including propofol, midazolam, α2 adrenoceptor agonists and opioids [9]. Propofol is a short-acting hypnotic agent used in children for induction and maintenance of general anesthesia [10]. Propofol has been used in different studies to decrease EA. Continuous infusion of propofol [11] and the administration of propofol at the end of procedure have been associated with decrease in the incidence of EA [12,13]. However, it has well known inconveniences and not preferred. Even lethal complications have been reported with a dose as low as 4.5 $mg.kg.h^{-1}$ after 3 days of administration [14,15].

There are few studies at the literature comparing the effect of propofol and sevoflurane in children and EA [16-19]. But they are limited with sample size and administration time and dose of propofol with no clear conclusion.

Thus, we tested the primary hypothesis that induction with propofol will decrease the incidence and intensity (severity) of emergence agitation when compared with sevoflurane. Secondary hypothesis, we

tested that postoperative pain after propofol induction will be lower than sevoflurane.

Methods

This prospective interventional study was conducted at Mustafa Kemal University Hospital, Turkey. The protocol was approved by the Hospital Ethics Committee (number 267, June 2012), and written informed consent was obtained from the parents of all enrolled children. The study used a double-blind methodology with random allocation to the two groups by a computer-generated list. The protocol was registered, Clinical Trials number NCT02110745.

We enrolled 116 American Society of Anesthesiologists Physical Status I-II children scheduled for elective inguinal hernia under general anesthesia over the course of two years. Patients were excluded in the presence of a genetic syndrome, allergy to propofol, neurologic disorder, and use of psychiatric medications and had undergone a series of recent general anesthesia.

Protocol

All patients were inpatients and followed standard fasting guidelines (no solids after midnight and unlimited clear liquids up to 2 hours before premedication). EMLA Cream (Lidocaine HCl, prilocaine, Astra Zeneca, Istanbul, Turkey) was applied to the hands of all the children one hour prior the induction of anesthesia. All the patients were also premeditated with midazolam hydrochloride 0.6 mg/kg orally one hour prior to the surgery. Intravenous cannula was inserted before arrival to the operating room. Heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2) were monitored in operating room. Patients were randomized into two groups using a computer-generated random number table; Group P (Propofol) and Group S (Sevoflurane). 0.25 mg/kg intravenous lidocaine was given to all patients in the induction of anesthesia. Anesthesia was induced with a bolus injection of 3 mg/kg propofol and maintained oxygen (FiO_2 0.50), nitrous oxide (FiO_2 0.50), 1-3% sevoflurane in group P. In group S, anesthesia was induced with oxygen (FiO_2 0.50), nitrous oxide (FiO_2 0.50), and sevoflurane (increasing concentrations up to 8%) via face mask and maintained with 1-3%. To facilitate intubation, 0.5 mg/kg rocuronium and 1 mcg/kg fentanyl were given to all patients. The concentration of sevoflurane was adjusted to maintain the heart rate and blood pressure within 20% of the pre-induction values. All the children received 12 ml/kg 5% dextrose in 0.45% normal saline solution during surgery. Same surgeon performed all the inguinal hernia procedures. No local anesthesia was used during the surgical procedure. At the skin closure, 15 mg/kg acetaminophen was given intravenously to all patients. At the end of the surgery, neuromuscular blockade was reversed with intravenous neostigmine 0.03 mg/kg and atropine 0.01 mg/kg. Anesthesia was discontinued, the stomach was suctioned, and the tracheal tube was removed when airway reflexes returned. The patients were transferred to the post anesthesia care unit (PACU). If agitation exceeded a score of 3 on the Agitation Cole Score [20] (Table1), 1 mcg/kg fentanyl was given intravenously. This score was used to calculate the incidence of agitation, where agitation scores of 1, 2 and 3 were regarded to represent absence of agitation, and scores of 4 and 5 were regarded to indicate presence of agitation. If pain exceeded score of 3 on the Wong-Baker FACES Pain Rating Scale [21], intravenous 15 mg/kg acetaminophen was given and first analgesic requirement time (discontinuation of the sevoflurane anesthesia to postoperative first analgesic need) was recorded. First transition from PACU to surgical ward was considered safe when patient had achieved a Modified Aldrete Score [22] 9 for at least 10 min, and SpO_2 95% with oxygen 2 l/min or 92% without oxygen, signified recovery of physical, mental, and physiological function to near preanesthetic levels. Postoperative nausea and vomiting (PONV) was treated with ondansetron 0.15 mg/kg intravenously. Patients were discharged only when they had no bleeding, no nausea and vomiting, were able to drink liquids, and had pain scores ≤ 2. Patients stayed at least 24 h in the hospital per surgical routine even in the absence of aforementioned parameters.

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

Table 1: Cole scoring system for emergence agitation.

Measurements

Demographic and morphometric characteristics were recorded. An anesthesiologist blinded to group allocation evaluated patients for postoperative agitation using Cole agitation scale at arrival in PACU, 10 min, 20 min, 30 min, 40 min, 50 min, 1 h and 2 h.

All the patients were assessed for pain intensity using the Wong-Baker Faces Pain Rating Scale at arrival in PACU, 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h.

Heart rate, mean arterial blood pressure, oxygen saturation, respiratory rate and side effects were recorded at arrival in PACU, 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h. Side effects including 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%), re-intubation, postoperative bleeding, and reoperation were recorded. Surgery time and duration of anesthesia (time from the induction to the discontinuation of sevoflurane anesthesia) were recorded. First analgesic requirement time was recorded. First eye opening, following first verbal command follow were recorded in operating room. Total PACU stay time, ambulation time (the time between PACU to first stand up) and first oral intake time were also recorded.

Furthermore, 10-point analogue scales were used to measure parents' satisfaction with their child's overall anesthetic and surgical care (0=not at all satisfied, 10=extremely satisfied).

Data Analysis

The sample size was designed to evaluate the difference in the incidence of EA during recovery. The sample size was determined assuming that the probability of propofol agitation was 30% and sevoflurane agitation was 55%. We wanted to find a significant difference ($P<0.05$) ($\alpha=0.05$, one tailed) with a power of 80% to detect a difference of 25%. Forty-seven patients per group would have been sufficient, but we expected some exclusions from the protocol (which did not happen) and increased this number to 58 (which allowed

finding the same significant difference with a power of 80%). For estimation of sample size, a preliminary study was performed [23]. Normal distribution of continuous variables was tested with Kolmogorov-Smirnoff test. Chi-square test was used for comparisons between categorical variables. Mann-Whitney U test and Students' T were used for comparison of groups for continuous variables. Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA) used. P<0.05 was considered significant.

Results

One hundred and sixteen parents consented patients who fulfilled the entry criteria were enrolled; all patients completed the entire study and were included the final analysis. There were no differences between groups in age, body weight, height, ASA physical status, durations of surgery and anesthesia (Table 2).

	Group S (n=58)	Group P (n=58)	P
Age (year)	3 (2-11)	4 (2-10)	0.081
Height (cm)	100 (50-140)	110 (60-163)	0.094
Weight (kg)	17 (10-35)	20 (11-50)	0.089
ASA	53/5	51/7	0.542
Duration of Surgery (min)	20 (10-120)	25 (10-150)	0.196
Duration of Anesthesia (min)	30 (18-145)	30 (15-110)	0.138
Results presented as numbers or median and range.			

Table 2: Baseline characteristics, Duration of surgery, duration of anesthesia.

The incidence of EA was significantly lower in the propofol group when compared with sevoflurane group at arrival in PACU (12 (20%) vs. 22 (37%), P=0.041), however there were no differences in other measurement times. But the cumulative incidences at the end of the postoperative two hours were statistically higher in sevoflurane group (38 (65.5%) vs. 23 (39.7%), p<0.005).

	Group S (n=58)	Group P (n=58)	P
PACU (0.h)	3 (2-5)	3 (1-5)	0.002
Postoperative 10 min	3 (2-5)	2 (2-5)	0.006
Postoperative 20 min	3 (2-5)	2 (2-4)	0.000
Postoperative 30 min	3 (2-4)	3 (2-4)	0.001
Postoperative 40 min	3 (2-4)	3 (2-4)	0.450
Postoperative 50 min	3 (2-4)	3 (2-4)	0.259
Postoperative 1 h	3 (2-4)	3 (2-4)	0.856
Postoperative 2 h	3 (0-3)	3 (2-3)	0.072
Results presented as numbers or median and range.			

Table 3: Postoperative agitation scores.

EA scores were significantly lower in propofol group in all measurements during postoperative 30 minutes (Table 3). Furthermore, fentanyl consumption at arrival in PACU and at the sum of the two hours was statistically lower in propofol group [(0 (0-35) vs. 0 (0-30), P=0.025) (14 (0-60) vs. 0 (0-60), P=0.019)].

Pain scores were significantly lower in the propofol group when compared with sevoflurane at all the measurement times (Table 4).

	Group S (n=58)	Group P (n=58)	P
PACU (0.h)	4 (2-8)	2 (0-8)	0.000
Postoperative 10 min	4 (2-6)	2 (0-6)	0.000
Postoperative 20 min	4 (2-6)	2 (0-6)	0.000
Postoperative 30 min	4 (2-4)	2 (0-6)	0.000
Postoperative 40 min	4 (2-6)	2 (0-6)	0.000
Postoperative 50 min	4 (0-6)	2 (0-6)	0.000
Postoperative 1 h	2 (0-6)	2 (0-6)	0.152
Postoperative 2 h	2 (0-6)	2 (0-4)	0.975
Postoperative 4 h	2 (0-4)	2 (0-4)	0.772
Postoperative 6 h	2 (0-4)	2 (0-4)	0.216
Postoperative 12 h	2 (0-4)	2 (0-4)	0.035
Postoperative 24 h	2 (0-2)	0 (0-2)	0.096
Results presented as numbers or median and range.			

Table 4: Postoperative pain scores.

Table 5 summarizes the speed and the quality of recovery from anesthesia. Sevoflurane provided a faster recovery as evidenced by the time to first spontaneous eye opening, first verbal command follow time and PACU staying time. Ambulation time, first oral intake time was all similar in both groups. Time to first analgesic dose was statistically shorter in sevoflurane group. The overall parents' satisfaction was higher in propofol group. PONV was the most common adverse event; there were no difference between the adverse events in postoperative 24h. Antiemetic consumption in postoperative 24h were also similar in both groups (4 (3%) vs. 3 (2%), p=1.000).

Discussion

The incidence of emergence agitation varies between 20-80% and is more frequently seen in young children and unrelated to gender [24,25]. According to previous studies the incidence of EA after propofol maintenance of anesthesia is between 0-9% [11-26]. The present study showed that the overall frequent incidence is lower in propofol group with a ratio of 39% and approximately 25% difference between two groups. Sun et al concluded that the incidence of EA was significantly higher in sevoflurane group when compared with propofol [27]. Because of different measurement techniques to quantify EA and differing methods of data analysis, the range of ratios accepted for EA is still really wide, makes the comparison of the results of these studies difficult. Time of scoring was another cause, because it is different in studies. Cole et al, [20] explained that the degree of EA is highly dependent on when it is measured.

There are fewer studies assessed both incidence and intense of EA together. This investigation demonstrates that the induction with propofol causes less incidence and intense of EA and postoperative pain when compared with sevoflurane.

	Group S (n=58)	Group P (n=58)	P
First spontaneous eye opening time (min)	5 (1-23)	10 (1-60)	0.008
First verbal command follow time (min)	10 (2-120)	15 (5-60)	0.004
PACU stay time (min)	18 (7-41)	25 (5-60)	0.000
Ambulation time (h)	8 (3-15)	6 (2-12)	0.143
First oral intake time (h)	4 (2-8)	4 (2-9)	0.118
First analgesic dose(ml)	245 (0-575)	292 (0-750)	0.485
First analgesic requirement time (min)	30 (2-180)	55 (5-180)	0.000
Parents satisfaction	8 (5-10)	9 (7-10)	0.000
Results presented as numbers or median and range.			

Table 5: Recovery parameters.

The etiology of EA after general anesthesia with volatile anesthetics is not clear yet. But the probable mechanism between children and EA is about variable rate of neurological recovery in brain and insufficient development of neurons [28]. But the most reasonable explanations for the mechanism of EA were rapid awakening with sevoflurane, desflurane, isoflurane [29,30] and postoperative pain sensation [31,32]. Sevoflurane is the most common well known aggravator anesthetic agent responsible for rapid emergence, with a dissociative state, that is, children awaken with altered cognitive perception [33,34]. The incidence of EA was lower in children after propofol anesthesia than sevoflurane [35]. Therefore, our results and the previous findings question the relationship between induction techniques and EA incidence and intense in children. The analgesic effect of propofol in proper induction doses as 3 mg/kg and fentanyl as 1 mcg/kg given together for all patients may be the probable causes of low incidence of EA in overall, preventing the pain sensation and low EA incidence in current study. It is well known that pain and opioid usage have been shown to change EA incidence [36]. We may only say probably because EA also occurs in pain-free procedures like imaging [37] and pain-free children with caudal analgesia [38]. Dahmani's meta-analysis supported our results that fentanyl is still preventative against EA following sevoflurane anesthesia [39]. In contrast Kararmaz et al [40] reported that fentanyl administration during the induction period does not reduce the incidence of EA. In our study, pain scores are not statistically significant in middle repeated measurement times because of the analgesic effects of fentanyl used as a requirement for EA in early postoperative period.

Postoperative pain scores were lower in postoperative period in propofol group. But it is really impossible to explain the underlying mechanisms simply. Because it may be about the analgesic properties of propofol or hyperalgesic effects of sevoflurane that both of them are recorded in the literature [41,42]. The relation between pain and emergence agitation really needs further investigations.

More emotional children who had difficulties in separation from their parents had higher EA incidence [20-43]. In current study all the patients were premedicated with oral midazolam, which creates inhibitory effects on the central nervous system. Midazolam premedication reduces sevoflurane-associated emergence agitation incidence by 40% [44]. In opposite the other study showed that it has no effect on EA after inhalational anesthesia in postoperative period [45]. But we know very well that midazolam has short duration of action like propofol. So we may explain how to reduce the incidence of EA with the residual effect or combination of the drugs. On the other hand preoperative anxiety is a well-known factor contributing to EA [39]. The effect of midazolam on emergence agitation is still controversial [11]. Maybe it reduces the overall agitation scores but we could not think the opposite, in our opinion mask induction technique is really difficult to accept for children without premedication.

When compared with sevoflurane contrarily propofol usage in children decreases the incidence of EA [28]. The rapid pharmacokinetics of propofol and the low doses (1 mg/kg) given in previous studies would explain why the bolus doses not achieve to prevent EA in induction [39]. Furthermore, 1 mg/kg propofol given after discontinuation of sevoflurane decreased the incidence of EA [10]. Cohen et al reported that induction with propofol 2 mg/kg at the beginning does not decrease EA, probably because of the short duration time of the propofol and low serum level not enough to suppress EA in acute postoperative period. But that is the point that these levels especially may be given after long procedures [35]. If the incidence of EA still reduces after long procedures, probably it may be about residual effect of propofol. Meta-analysis reported that timing in administration is important. Especially continuous administration and a bolus dose at the end of anesthesia were protective because of propofol concentration during emergence [39]. We could not measure the concentration but our study group inguinal hernias are not such long surgical procedures. Propofol, gamma (γ)-aminobutyric acid-A (GABA-A) receptor inhibitor, produces a positive mood or euphoric state postoperatively in adults [46,47].

Tan et al concluded that patients anesthetized with propofol have less postoperative pain compared with sevoflurane in acute postoperative period [48]. Fentanyl is an important opioid routinely used in induction of children. Propofol bolus with fentanyl may prolonged the efficacy of propofol, with the effect of midazolam given in the premedication [2,36]. Likewise there are several studies with lower incidence of EA in propofol group with longer recovery times when compared with sevoflurane [49]. Longer recovery times can be due to residual sedative effect of propofol in the early recover period as well [16]. The recovery times has opposite correlation with agitation scores [50]. First eye opening, first verbal command follow, PACU staying time were shorter in sevoflurane group. It was really important to measure the depth of anesthesia in such conditions because the comparison between propofol and sevoflurane in this regard is really complicated. Rapid awakening in an unfamiliar environment for psychologically underdeveloped children is another major cause of EA [49].

Adverse events may cause EA like hypoxemia, bladder distension, nausea and pain. None of the patients experienced hypoxemia and bladder distension but a few of them had nausea. The most common adverse event in children in postoperative period is nausea and vomiting [51]. Fentanyl and nitrous oxide was used in the same doses in both groups. In current study we gave all patients ondansetron as antiemetic routine. May be it suppressed the reducing effect of

propofol about PONV, because there was no statistical difference between two groups. But may be children felt pain however we could not measure, fentanyl given, nitrous oxide cause this adverse effect in a few of them.

Viitanen et al. [52] concluded that the induction of propofol and continued with sevoflurane causes quiter state during acute recovery period. And also it is well known that propofol has sedative and euphoric effects in adults in postoperative periods [46,47] which causes better agitation scores in children during postoperative period. At the same this calmer state may cause the difference between two groups in parents' satisfaction as in current study. Parents' satisfaction was really high in propofol group when compared with sevoflurane.

The current study has several limitations. More than 16 rating scales have been used to measure EA [53]. The major lack of the study like the most of the others done before, we used simple graded measurement [49,28]. It was important that only one blinded observer graded all scores. We also used hemodynamical variables to indicate comparable depths of anesthesia intraoperatively, although these variables are not reliable for monitoring the depth of anesthesia. The patients under 2 years of age were all excluded, because of difficulties in evaluation of emergence agitation state in them. The doses of propofol and sevoflurane are accurate for induction but they are not equipotent in fact. Lidocaine HCl is the most used medication for pain relieve before propofol injection. This medication may achieve preemptive analgesia and reduction of airway reflexes in pediatric patients. So it may cause less EA, from the other aspects it prevents the increase of EA incidence related with propofol pain [54,55].

We concluded that induction with propofol in accurate dose may be effective in reducing the incidence and intense of EA in children undergoing inguinal hernia surgery between 2-12 years old. Propofol may be preferred as an agent in induction for all children undergoing operations with general anesthesia. Future studies should focus on associations of pain and EA.

Conflicts of Interest

The authors declare no conflicts of interest.

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