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The effect of intravenous paracetamol on emergence agitation in preschool-aged children under sevoflurane anesthesia for strabismus surgery

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Abstract

Background: Emergence agitation (EA), a clinical phenomenon characterized by negative behaviors, is commonly observed in preschool-aged population. Paracetamol is a frequently preferred analgesic for postoperative pain in pediatrics due to low adverse effect profile. However, the preventive or therapeutic effectiveness of intravenous (IV) paracetamol on EA has not been fully elucidated, particularly in preschool-aged children. This study aimed to demonstrate the efficacy of IV paracetamol on EA in children who underwent strabismus surgery.

Methods: Twenty seven patients were divided into two groups; preschool-aged children between 2 and 6 years old (Group 1) and children > 6 years old (Group 2). After anesthesia induction and before the surgical incision, IV paracetamol (10 mg/kg) was given to all cases. Face, Legs, Activity, Cry, and Consolability (FLACC) scale was used to assess the postoperative pain level while EA was evaluated using the Pediatric Anesthesia Emergence Delirium (PAED) scale. The two groups were then compared each other in terms of FLACC and PAED scores.

Results: THere were 15 and 12 patients in Group 1 and Group 2, respectively. No significant differences in FLACC and PAED scores were found similar between the two groups ($p>0.05$). The number of patients with ED was similar between the groups ($p>0.05$).

Conclusions: IV paracetamol was found effective in the management of postoperative pain and EA in preschool-aged children who underwent strabismus surgery with sevoflurane anesthesia.

Keywords: Emergence agitation, ıntravenous paracetamol, pediatric anesthesia, sevoflurane, strabismus surgery

Introduction

Emergence agitation (EA), first described in 1960s, is a clinical phenomenon characterized by various negative behavioral disorders such as crying, moaning, sobbing, thrashing, excitation, incoherence, and disorientation [1, 2]. This annoying clinical entity is more common in pediatric patients compared to adults, with a reported incidence of up to 80% [3]. Although the exact etiology is unclear, several risk factors including postoperative anxiety and pain, type of surgical procedures, physical stimulation, stressful induction, hypoxemia, and anesthetic medications have been found to be associated with this phenomenon [4]. Among those, sevoflurane, an inhalation anesthetic, has been most commonly accused risk factor for the development of EA [5]. However, sevoflurane is widely preferred in daily anesthesia management due to the rapid onset and offset profiles, less airway irritation, and less impairment of cardiac functions [6, 7]. For this reason, most recent studies have focused on determining the efficacy of various single and/or combined drug applications, such as paracetamol, dexamethasone, tramadol, and dexmedetomidine in preventing this entity [5, 8-10]. However, paracetamol, among those drugs, is mostly preferred in routine clinical practice due to its safety profile. In the current literature, there is insufficient data regarding the efficacy of intravenous (IV) use of this drug on postoperative EA, particularly in preschool-aged group.

The present study was designed to investigate the safety and effectiveness of IV paracetamol on postoperative pain and EA in little children who underwent strabismus surgery.

Materials and Methods

Patients: The study was approved by Institutional Ethics Committee (permit No/Date: 07/2020), and was conducted in accordance with the Helsinki Declaration. A total of 27 pediatric patients who underwent elective strabismus surgery under general anesthesia at Eskişehir Osmangazi University Hospital were included in the study. Informed consents were obtained from the patients and/or their relatives preoperatively. Patients' age, gender, and American Society of Anesthesiologist (ASA) physical status, surgical data, all anesthetic and analgesic drugs, perioperative anesthesia-related complications were noted. Exclusion criteria were being under two years old, ASA physical status of 3/4, significant renal, hepatic, or cardiorespiratory disease, mental or development delay, and allergy to any drug. The patients were divided into two groups according to age; preschool-aged children between 2 and 6 years old (Group 1) and children > 6 years old (Group 2). Basic characteristics, postoperative pain and EA scores were compared between the groups.

Anesthetic management: The fasting time before operation was set as at least six hours. No premedication was given to patients. On the way to the operating room (OR), a separation score was used to determine the emotional state of the child at the time of separation from the parent: 1 (excellent, separates easily), 2 (good, whimpers and calms with reassurance), 3 (fair, cries, not clinging, not staying calm), and 4 (poor, cries and clings to parent) Category 1-2 meant satisfactory, while category 3-4 was considered unsatisfactory [11].After standard monitorization, induction of anesthesia was performed via a face-mask with sevoflurane (8-5-3%) in oxygen (4 L/min) and nitrous oxide (50%-50%). Following adequate lost of consciousness, IV access was established and airway control was provided by laryngeal mask airway (LMA) with the administration of IV remifentanil (0.5-1 mcg/kg) plus lidocain (0.5 mg/kg) plus propofol (3-4 mg/kg). After induction and before surgical incision, IV paracetamol (10 mg/kg) was given to all children. For anesthesia maintenance, patients received sevoflurane (2-3%) in 4 l/m 50% N_2O and 50% O_2.

Hemodynamic parameters including heart rate (HR), mean arterial pressure, oxygen saturation (SpO_2), and end-tidal carbondioxide ($ETCO_2$) were continuously monitored during the surgical procedure. In all patients, time of awakening (from end of surgery to getting out of the OR) was noted. The children were observed in the recovery room for at least half an hour. The modified Aldrete scores (MAS) were calculated at 5-minute intervals. Hemodynamics were also recorded during the recovery period. The children were transferred to inpatient clinic when their MAS achieved score of 9.

Assesment of postoperative pain and emergence agitation: After getting out of OR, postoperative pain and EA were assessed at 5, 10, 15, and 20. minutes in the recovery yard. EA was also assessed while the patient was getting out of OR. Postoperative pain level was measured by Face, Legs, Activity, Cry, and Consolability (FLACC) scale, scores ranging from zero to ten [12]. Pain was considered to be present in case of a maximum FLACC score of 4 or above.

EA was evaluated by the Pediatric Anesthesia Emergence Delirium (PAED) scale, consisting five psychometric items and scoring from 0 to 20 [13]. Maximum PAED score of 12 or above was considered emergence delirium (ED), (Table 1).

Table 1: PAED scale for evaluation of emergence agitation

Behaviour	Not at all	Just a little	Quite a bit	Very much	Extremely
Makes eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

Statistical analysis

A power analysis based on a previous study [14] showed that a sample size of 6 patients per group was required to achive a power of 100% with a significant level of 5% to evaluate the difference of PAED scores between the groups. Data analyses were performed using The Statistical package for social science (SPSS 23.0 software, IL-Chicago-USA). Descriptive analyses were presented as number (%) and mean±standard deviation for categorical and continuous variables, respectively. Chi-squre test, Mann Whitney U test, and Fisher's exact test were used to assess the differences between the groups. A p value under 0.05 was accepted as significant.

Results

Twenty-seven children with a mean age of 5.7 years old were included in the study. There were 18 (66.7%) boys and 9 (33.3%) girls. All patients were operated on the diagnosis of strabismus under sevoflurane anesthesia using LMA. Anesthesia technique and medications were standard. IV paracetamol was used for postoperative analgesia. The patients were divided into two groups; preschool-aged children between 2-6 years old (Group 1, N= 15) and children > 6 years old (Group 2, N= 12). All surgical procedures were successfully completed. No significant complication or mortality developed during perioperative period. On the other hand, mild intraoperative bradycardia developed in four children (two in each group). The basic characteristics and clinical data of the study population were presented in Table 2.

Table 2: Basic patient characteristics and clinical data (N=27)

Characteristics	n (%)
Age (y)	5.7±2.5 (2-11)
Gender (Female/Male)	12 (33.3%)/15 (66.7%)
ASA score	
ASA 1	22 (81.5%)
ASA 2	5 (18.5%)
Operation time (min)	31.5±8.7 (18-50)
Anesthesia time (min)	36.4±8.9 (20-55)
Airway instrument (LMA)	27 (100%)
Induction (Propofol plus remifentanil plus sevofluran)	27 (100%)
Maintenance (sevoflurane)	27 (100%)
Complication	4 (14.8%)

Data are presented as mean±SD for age, operation time, and anesthesia time; n (%) for other variables. y: year, min: minute, LMA: Laryngeal mask airway

The two patient groups were statistically similar in terms of gender, ASA score, separation score, anesthesia time, operation time, and time of awakening (Table 3).

Table 3: Comparison of basic characteristics between the two groups

Characteristics	Group 1 (N=15)	Group 2 (N=12)	P
Age (Y)	3.8±1.6 (2-6)	8.0±1.3 (7-11)	< 0.001
Weight (Kg)	16.1±5.1 (10-30)	27.6±7.5 (18-45)	< 0.001
Gender			1.000
Female	5 (33.3%)	4 (33.3%)	
Male	10 (66.7%)	8 (66.7%)	
ASA score			0.825
ASA 1	12 (80%)	10 (83.3%)	
ASA 2	3 (20%)	2 (16.7%)	
Separation score			0.030
Satisfactory (score 1-2)	12 (80%)	11 (91.7%)	
Unsatisfactory (score 3-4)	3 (20%)	1 (8.3%)	
Operation time (min)	31.6±8.5 (20-45)	31.5±9.3 (18-50)	1.000
Anesthesia time (min)	36.6±8.5 (25-50)	36.2±9.7 (20-55)	1.000
Time of awakening (min)	6.3±2.2 (4-12)	6.0±2.8 (2-13)	0.755
Complication	2 (13.3%)	2 (16.6%)	1.000

Data are presented as mean±SD for age, weight, operation time, anesthesia time, and time of awakening; n (%) for other variables. Y: Year, Kg: kilogram, Min: Minute

At 5, 10, 15, and 20. Minutes in the recovery room, FLACC scores for postoperative pain level, PAED scores for postoperative EA status, and MASs were compared between the two patient groups (Table 4). No significant differences in all scores were found between between group 1 and group 2 (*p*>0.05). The time of MAS to reach 9 was also statistically similar the groups (P=0.548).

Table 4: The comparison of FLACC scores, PAED scores, and MASs between the groups

	Group 1 (N=15)	Group 2 (N=12)	P
FLACC 5	2.9±3.3 (0-8)	0.6±2.3 (0-8)	0.067
FLACC10	2.2±2.9 (0-8)	0.9±1.9 (0-6)	0.374
FLACC15	3.6±3.3 (0-10)	3.2±2.1 (0-6)	0.867
FLACC20	3.1±4.0 (0-9)	2.0±2.1 (0-5)	0.876
PAED5	5.2±6.0 (0-16)	1.0±3.4 (0-12)	0.059
PAED10	5.0±5.7 (0-16)	0.8±2.8 (0-10)	0.085
PAED15	7.8±6.6 (0-18)	5.9±4.5 (0-13)	0.456
PAED20	5.1±6.7 (0-17)	5.4±6.7 (0-15)	1.000
MAS5	5.4±1.7 (1-8)	5.6±1.0 (4-7)	0.867
MAS10	6.5±2.3 (1-10)	6.7±1.4 (4-9)	1.000
MAS15	7.6±2.7 (2-10)	8.4±1.2 (6-10)	0.867
MAS20	6.2±3.0 (2-9)	8.1±1.3 (6-9)	0.295
Time of MAS to reach 9	18.8±6.7 (10-30)	17.4±6.6 (10-30)	0.548

The patient groups were also compared each other in terms of the presence of ED (Table 5). In Group 1, two children (13.3%) developed EA at 20th minutes in the recovery yard while three (20%) had EA at 5th minutes. On the other hand, only one (8.3%) child in group 2 was diagnosed with ED at 5th and 20th minutes in the recovery room.

Table 5: The comparison of emergence delirium between the groups

	Group 1 (N=15)	Group 2 (N=12)	P
Emergence delirium (5th Min.)	3 (20%)	1 (8.3%)	0.605
Emergence delirium (10th Min.)	3 (20%)	1 (8.3%)	0.605
Emergence delirium (15th Min.)	5 (33.3%)	2 (16.6%)	0.408
Emergence delirium (20th Min.)	2 (13.3%)	1 (8.3%)	1.000

Discussion

EA, especially following pediatric operations, is common, and poses an important challenge for anesthesia providers. Although this entity usually limits itself within the first half hour of recovery period, it may last up several days [7]. Prolongation of this situation is associated with a number of serious problems, such as physical damage to the wound dressing or other surgical instruments such as drains and catheters, raising concerns of parents, need of more sedative and analgesic drugs, and increased health costs related to prolonged recovery and hospitalization time [4, 7, 15]. Therefore, sufficient knowledge of this phenomenon, higher clinical attention, minimizing possible causative factors, and necessary and timely medications are of great importance in preventing or reducing EA-related negative situations. However, no specific medication or preventive method has been determined to date [16].

In recent years, most of the clinical studies have investigated the potential preventive or therapeutic effects of some drugs, particularly analgesics, on this entity; because, postoperative pain status together with preschool-aged population and ophthalmologic or otolaryngologic procedures was determined as a significant risk factor for EA [5, 9, 17]. To date, the effectiveness of various analgesic agents including paracetamol, non-sterodal antiinflammatory drugs (NSAIDs) and opioids on the development of EA have been evaluated. However, several aspects such as higher complication rates and age restrictions limited wide use of those drugs. For instance, increased risk of postoperative bleeding is the main limitation of NSAIDs [18]. Tramadol, a synthetic opioid analgesic, provides an effective analgesia; however, its potential side effects such as nausea, vomitting, and respiratory depression are the primary concerns of its wide use [19]. In addition, tramadol is not recommended to be use for postoperative analgesia in pediatric population. On the other hand, paracetamol is known as a safe analgesic and antipyretic, with low adverse effects on the cardiovascular or respiratory system. It also has no effect on hematological functions, and does not cause gastric irritation. Although paracetamol alone has been reported to be inadequate in the management of postoperative analgesia, it is often preferred in routine practice due to its low adverse effect profile, particularly in pediatrics [20].

Paracetamol can be administered in different ways such as oral, rectal and IV. Oral and rectal administrations take longer time to provide peak pain relief, compared with IV root. In parallel, IV formulation of paracetamol was shown as an attractive option for the treatment of postsurgical pain [21]. The results obtained from our study also supported this positive finding. According to FLACC scoring, only seven and three patients in our study had "pain" at 5th and 20th minutes, respectively. All mean FLACC scores in both groups were also under score of 4, which meant that preemptive IV paracetamol was effective for providing early postoperative analgesia in both preschool-aged and older children. However, the effectiveness of IV paracetamol on EA has not been clearly demonstrated particularly in preschool-aged group.

In pediatric population, there are few clinical studies compared paracetamol and other different analgesics in terms of postanesthetic EA [9, 22, 23]. Moreover, to our knowledge, there is no study investigated the effectiveness of IV paracetamol on EA between different pediatric age groups. It should be also noted here that, the majority of the similar studies were mostly conducted on school-aged or older children. However, this age distribution is important since EA is most commonly seen in preschool-aged children. In addition, not only IV form but also oral or rectal forms of paracetamol were used in those studies. Moreover, most of such studies were conducted on patients who underwent head and neck surgeries such as adenotonsillectomy [5, 9, 22]. However, opthalmatological procedures are among the most common surgical interventions causing EA. Finally, in some studies, the patients were premedicated with oral midazolam before surgery [23]. It should be stated here that midazolam is an effective anxiolytic, and provides a sedation that may affect postoperative agitation and pain scores [24]. In our anesthesia practice, we do not use any premedication due to our routine approach and the potential respiratory risks. For all these reasons, demonstrating the safety and efficacy of IV paracetamol in younger age children undergoing strabismus surgery is of great importance for its daily use. The results obtained from the present work demonsrated that IV paracetamol provided similar postoperative analgesia in preschool-aged group and older group. In parallel to FLACC scores, postoperative EA scores were also similar in both groups. Although different incidences of ED were reported due to age differences or different definitions of the minimum PAED score required to diagnose ED, the incidence of ED in our study was generally consistent with the literature [3, 25]. Although not statistically significant, the incidence of ED was higher in preschool-aged patients compared to others, in parallel to the FLACC and PAED scores. This finding was also compatible with general information in the literature indicating higher incidence of EA in preschool-aged group [3, 5]. As an interesting finding of our work, the incidence of ED increased at 15th minutes of recovery and then decreased at 20^{th} minutes. This situation may be related to the decreased anesthetic effect and increased alertness. We suggest that the higher incidence of ED in the preschool-aged group, although not significant, can be explained by the fact that these children feel hunger than other children and realize that their parents are not with them.

The present study had several limitations. Firstly, it was conducted in a single center, which may limit the generalizability of the results. A relatively, but not statistically, small number of patient groups may be another limitation, which makes it difficult to interpret subgroup findings. However, we suggest that the results obtained from our study may contribute to fill the gap regarding this important issue in the current literature since there is insufficient data on the efficacy of IV paracetamol use on postoperative EA especially in preschool-aged patients.

Conclusion

According to the results obtained from the present study, postoperative pain levels and EA status are similar between preschool-aged patients and older pediatric patients. The complication rates were also similar between both groups. Therefore, IV paracetamol may be suggested as a safe and effective option for the management of postoperative pain and EA in preschool-aged children who underwent strabismus surgery.

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