Effect of Intravenous Fentanyl Given Prior to the End of Surgery on Emergence Agitation in Pediatric Patients

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Objective: *Evaluate the effect of intravenous fentanyl on the incidence and severity of EA.*
Material and Method: *In the clinical trial, 144 patients aged between two and nine years, scheduled for elective surgery were enrolled and randomly assigned to receive either fentanyl 1 µg/kg or normal saline 1 ml/10 kg, 15 minutes before the end of surgery. Watcha's behavioral emergence delirium scale was used to assess EA.*
Results: *The incidence of EA was lower in the fentanyl group (11/72 vs. 23/72 person respectively, p = 0.03). However, there was no statistically significant difference in the number of patients with severe EA (1/72 vs. 6/72 person respectively, p = 0.12). Fewer number of patients in the fentanyl group had moderate to severe pain when compared with the control group (16/72 vs. 30/72 person respectively, p = 0.02). The number of patient who required rescue analgesia was significantly lower in the fentanyl group (18/72 vs. 30/72 person respectively, p = 0.04). There were no statistically significant differences in terms of emergence time, postoperative adverse events, and length of stay in the post-anesthetic care unit between the two groups.*
Conclusion: *Administration of intravenous fentanyl 1 µg/kg 15 minutes prior the end of surgery decreased the incidence of EA and reduced pain without delaying emergence and without any increase in postoperative complications.*

Keywords: *Emergence agitation, Pediatric, Fentanyl*

J Med Assoc Thai 2013; 96 (12): 1556-62
Full text. e-Journal: *http://www.jmatonline.com*

Emergence agitation (EA) is a common self-limiting problem after emerging from general anesthesia (GA), especially in pediatric patients[1,2]. The incidence of EA in children ranges between 10 and 67%[3-5]. For patients given short-acting volatiles such as sevoflurane, the incidence of EA can be even higher[5-7]. Children who have EA will be inconsolable, irritable, uncooperative, and disoriented[1]. Severe cases of EA can cause self-harm and develop postoperative behavioral changes[8].

Previous studies have reported that rapid emergence, inadequate pain control, volatile anesthetic agents, preschool age, preoperative anxiety, no previous history of surgery, otolaryngologic, and ophthalmologic surgery are positive predictors of EA[6,9,10]. While using midazolam[11], clonidine[11], intravenous induction agents such as propofol[12], dexmedetomidine[13], ketamine[14], narcotic medication[15,16], 5-HT_3 antagonist[17], and nitrous oxide[18], seem to reduce the incidence of EA.

Cravero et al demonstrated that intravenous fentanyl 1 µg/kg given to pediatric patients who underwent MRI under sevoflurane anesthesia could decrease the incidence of EA by 43.8%[16]. However, no study focused on severity of EA. The present study hypothesis was that administration of intravenous fentanyl 1 µg/kg given 15 minutes before the end of surgery would reduce both the incidence and severity of EA.

Material and Method

After being approved by the ethics committee, a randomized double-blinded study was conducted in Songklanagarind Hospital between April 2010 and July 2011. One hundred and forty-four inpatients aged between two and nine years old, ASA physical status I-III and scheduled for elective surgery under general anesthesia (GA) were included in the study after obtaining the consent from their parents. Exclusion criteria were ASA physical status IV-V. Patients were randomly divided by computer into two groups (72/group), fentanyl (F) and normal saline (N).

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The group type was sealed in opaque envelopes that were opened only after the subject was recruited (Fig. 1). Attending nurses who prepared the drugs and the anesthesiologist who took care of the patient intraoperatively were not involved in the evaluating process. All investigators were trained on how to score the EA evaluation.

Before surgery, demographic data and patient characteristics were collected. The standard premedication was given. A four-point separation scale[13], 1 = excellent (separates easily), 2 = good (not clinging, whimpers, calms with reassurance), 3 = fair (not clinging, cries, will not calm or quieten), 4 = poor (cries, clinging to parent) was used to evaluate the child's behavior during separation from parents and once again after arrival into the operating room. During the induction, an induction anxiety scale[19] 1 = excellent (unafraid, cooperative, accepts mask readily), 2 = good (slight fear of mask, easily calmed with reassurance), 3 = fair (moderate fear, not calmed with reassurance), 4 = poor (terrified, crying, agitated) was used to evaluate the patients. An induction scale of 1 or 2 was classified as satisfactory and a scale of 3 or 4 was classified as unsatisfactory. The baseline vital signs were recorded. Fentanyl 1 µg/kg, thiopental 6 mg/kg and cisatracurium 0.15 mg/kg were used for induction. Air, oxygen, and sevoflurane were used for maintenance. After starting the surgery, vital signs were recorded every five minutes. Fentanyl would be given at a dosage of 0.5 µg/kg if the heart rate and mean arterial blood pressure increased more than 15% from the baseline. A repeated dose would be given if vital signs did not return to the baseline level after 5 minutes.

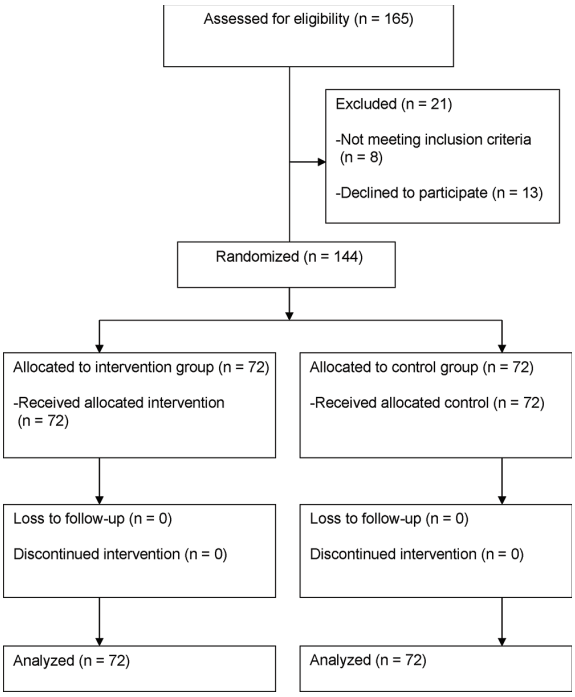

Fig. 1 Consort flow diagram.

At 15 minutes before the end of anesthesia, intravenous fentanyl 1 µg/kg (concentration10 µg/ml) was given to patients according to the intervention group while the same amount of normal saline (1 ml/10 kg) was given to patients in the control group.

Vital signs, type of operation, end tidal sevoflurane ($EtCO_2$), awakening duration (measured as the time elapsed from turning off volatile agent to the removal of airway device), duration of anesthetic, and intraoperative adverse event were recorded by the attending nurse.

At the post anesthesia care unit (PACU), emergence behavior was observed by the attending PACU nurses. At five minutes after arrival in PACU, the Watcha behavioral scale (1 = calm, 2 = crying but can be consoled, 3 = crying, cannot be consoled and 4 = agitated and thrashing around) was used to assess EA[20]. Emergence scores of 3 or 4 were classified as having EA. A score of 4 was considered as severe EA. The duration of EA and any treatment given were also recorded. Pain scores were evaluated using the FLACC (face, legs, activity, cry, consolability) pain scale for patients aged less than 5 years old. For patients aged more than 5 years, a numerical pain scale was used. A pain score higher than 3 was classified as moderate to severe pain. The length of stay in PACU and PACU adverse events were recorded.

The primary outcome of this study was the incidence of EA. Secondary outcomes were severity of EA and postoperative adverse events. The sample size was determined according to a previous study of EA in Thai pediatric patients, which indicated the incidence of EA of 43.2%[6]. We assumed that the incidence of EA would decreased by more than 50% in the intervention group when compared with the control group. The data was analyzed using R. Continuous data and compared using Student's t-test. For categorical data, Pearson's Chi-squared or Fisher's exact test was used. A p-values of less than 0.05 was considered to be statistically significant.

Results

One hundred forty four patients were recruited in the present study. There were no statistically

significant differences in terms of age, sex, ASA physical status, type of operation, history of previous surgery, separation anxiety, and anxiety level at induction between the intervention and control group (Table 1). The mean ages of the patients in the intervention and control groups were 5.67±2.43 and 5.23±2.20 years, respectively. Seven patients in the intervention group and nine patients in the control group had separation anxiety. Anxiety during the induction period was diagnosed in six patients in both groups.

The incidence of EA was lower in the intervention group compared with the control group (11/72 vs. 23/72, p = 0.03). One patient (1.4%) from the intervention group and six patients (8.3%) from the control group had severe EA (p = 0.12). A few number of patients in the intervention group had moderate to severe pain when compared with the patients in the control group (16/72 vs. 30/72, p = 0.02). There were no correlations between EA and preoperative anxiety including separation anxiety and anxiety at induction period (p = 0.75 and 0.13, respectively). Subgroup analysis also showed that there were no relationships between the patient who had high preoperative anxiety level (separation anxiety and induction anxiety scale = 4) and the severity of EA (p = 1.00 in both group). The awakening time among patients in the control group was shorter than for those in the fentanyl group (12.60±6.50 vs. 15.97±11.48 minutes, p = 0.54). There were no statistically significant differences in terms of postoperative complications and PACU stay between the two groups (Table 2, 3).

The seven patients with severe EA patients needed both pharmacologic and non-pharmacologic treatment (reposition and/or parental present). The duration of severe EA ranged between five and 45 minutes after emergence from anesthesia. There was no statistically significant differences in terms of awakening time and PACU stay between patients who had severe and non severe EA (p = 1.00 and 0.67,

Table 1. Demographic data and sample characteristics

Patient characteristic	Group		p-value
	Fentanyl (n = 72)	Normal saline (n = 72)	
Mean age, year (SD)	5.67 (2.43)	5.23 (2.20)	0.25
Sex: male, n (%)	39 (54.2)	42 (58.3)	0.74
Mean body weight, kg (SD)	19.76 (7.89)	18.59 (8.51)	0.38
ASA, n (%)			0.79
I	25 (34.7)	22 (31.0)	
II	46 (63.9)	47 (66.2)	
III	1 (1.4)	2 (2.8)	
Previous surgery, n (%)	33 (45.8)	42 (58.3)	0.18
Separation anxiety (score >2), n (%)	7 (9.7)	9 (12.5)	0.79
Anxiety at induction period (score >2), n (%)	6 (8.3)	6 (8.3)	1

ASA = American Society of Anesthesiologists

Table 2. Characteristics of the emergence and recovery phase in the post anaesthesia care unit

Characteristics	Group		p-value
	Fentanyl (n = 72)	Normal saline (n = 72)	
Emergence agitation (EA), n (%)	11 (15.3)	23 (31.9)	0.03
Severe EA, n (%)	1 (1.4)	6 (8.3)	0.12
Mean time to awakening, min (SD)	15.97±11.48	12.60±6.50	0.54
Mean PACU time, min (SD)	48.33±14.59	46.75±17.43	0.34
Mean pain score, point (SD)	1.84±3.02	3.61±3.66	0.29
Moderate to severe pain (pain score ≥4), n (%)	16 (22.2)	30 (41.7)	0.02
Rescue dose needed, n (%)	18 (25.0)	30 (42.9)	0.04

PACU = post anesthesia care unit

Table 3. Postoperative adverse events

Adverse event	Group	
	Fentanyl (n = 72) n (%)	Normal saline (n = 72) n (%)
Drowsiness	6 (8.3)	5 (6.9)
Hypoxemia	0 (0)	1 (1.4)
Nausea/vomitting	1 (1.4)	3 (4.2)
Upper airway obstruction	0 (0)	2 (2.8)
Reintubation	0 (0)	0 (0)

respectively). Four out of the seven patients who had severe EA had severe pain. Two patients still had EA after adequate pain control. PACU time was significantly longer in the patients who had moderate to severe pain compared with the patients who had mild pain (45.32±13.76 and 52.28±19.37 minutes, respectively, p = 0.02). The number of patients who required rescue analgesia in the PACU was significantly lower in the fentanyl group (18/72 and 30/72 persons, respectively, p = 0.04). Severe EA and moderate to severe pain were found to be significantly correlated (16/72 vs. 30/72 persons, respectively, p = 0.02).

Discussion

The results of the present study show that intravenous fentanyl 1 µg/kg given 15 minutes before the end of surgery could reduce the incidence of emergence agitation. The study finding was consistent with the study by Cravero et al[16]. However, the meta-analysis by Dahmani et al[22] showing fentanyl was effective in reducing EA particularly if sevoflurane was used and only intranasal route exhibit a preventive effect against EA whereas IV fentanyl did not. The mechanism of action of fentanyl on EA is still unknown.

There were no correlations between EA and preoperative anxiety including separation anxiety and anxiety at induction period. This study finding was consistent with the previous study by Bong[3] and Voepel-Lewis[4]. The previous study by Kain[8] reported that the marked symptoms of EA increased by 10% for each increment of 10 points in the child's state anxiety score (mYPAS). However, the present study's results show that there were no relationships between the patient who had severe EA and preoperative anxiety level. The tools used to evaluate preoperative anxiety level in this present study had fewer items than mYPAS scale. In turn, less aspects of preoperative anxiety were evaluated in this study and it could affect the study results.

Fewer patients in the fentanyl group had moderate to severe pain and a few required rescue analgesic medication when compared with the control group. In the present study, four out of the seven patients who had severe EA had severe pain. After adequate pain control, two patients still had EA. The mean dose of fentanyl used prior the intervention was 2.68±0.72 µg/kg compared to the study by Cohen(15,23), which demonstrated that the various doses of intravenous fentanyl ranging between 1.25-2.5 µg/kg were safe and effective for EA prevention in moderately painful procedures. The surgical procedures in this study varied from mildly painful procedures to severely painful procedures. Therefore, there might have been some patients in this study that had inadequate pain control especially in severely painful procedures. There is the difficulty of differentiating pain from emergence agitation. The patient who had pain expressed this by crying in combination with agitation. Crying, agitation, and thrashing around were present in the Watcha's Behavioral Emergence Delirium scale, which made it difficult to distinguish between pain and severe EA at the time of evaluation.

In terms of severity of EA, there was no difference between the two groups. In two previous studies, Cravero and Galinkin[16,24] reported that intravenous and intranasal fentanyl administration could reduce the incidence of EA but these studies did not focus on the severity of EA. A previous study by Lankinen[17] showed that tropisetron (a 5 HT_3 antagonist) could also reduce the incidence of EA. Cohen et al[15] demonstrated that intravenous fentanyl given intraoperatively could reduce the incidence of EA without any effect on the severity of EA. However, in the Cohen study, a 5 HT_3 antagonist was given to the patient, which could affect the severity of EA. In the present study, some factors could affect the EA scoring. Firstly, the difficulty of differentiating pain from emergence agitation as mentioned above. Secondly, the remaining effect of premedication in very short surgical procedures could affect the EA scoring at the time of evaluation.

There were no differences in terms of severity of EA between the intervention and control groups. 1.4% of patients in the fentanyl group had severe EA compared with 8.3% in the control group. Kain et al[8] reported that patients who had marked EA (thrashing and/or needs restraint and/or constant crying) tended

to have a new onset of postoperative maladaptive behavioral change (odds ratio 1.43) which could affect long-term quality of life. Fentanyl might therefore reduce the incidence of EA. However, there still needs further investigation to confirm this result. There were no differences in incidence of adverse events between the two groups. The result was comparable with others studies[16,19]. The dose of fentanyl used in this study was lower when compared with the study by Cohen[15] which reported that fentanyl 2.5 µg/kg was safely used for prevention of EA.

There were some limitations in this study. Firstly, there are many evaluation scales to evaluate EA. The Pediatric Anesthesia Emergence Delirium (PAED) scale, which is a well-validated scale, was not selected by the authors due to the complexity of the scale and no exact cut off point to determine EA. The scale used in the present study, Watcha behavioral emergence delirium scale, was reported as having greater sensitivity and specificity compared with PAED scale >10[21]. Secondly, the sample size of this study was calculated using the incidence of EA, which may be higher than the incidence of severe EA.

In conclusion, intravenous fentanyl administration prior the end of surgery could decrease the incidence of EA and postoperative pain without any increase in postoperative complications.

What is already known on this topic?

Pediatric anesthesiologists are now turned to the issue of EA with concern. A child who develops severe EA post-operative tends to have post-operative behavioral changes that could affect the child directly as well as the parents. Some anesthetic agents such as propofol, dexmedetomidine, ketamine, and intranasal fentanyl have been reported to reduce the incidence of EA.

What this study adds?

The present study's results support that intravenous fentanyl given prior the end of surgery is effective in reducing the incidence of EA. However, in terms of the severity of EA, which was found to be related to post-operative behavioral changes, further investigation is still needed to confirm the results.

Potential conflicts of interest

None.

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ผลของการให้ยาเฟนตานิลทางหลอดเลือดดำก่อนเสร็จผ่าตัดต่อการเกิดภาวะกระวนกระวายในเด็ก

งามจิตร์ ภัทรวิทย์, มลิวัลย์ ออฟูวงศ์, แสงเดือน คลายนา, ปัณญวีร์ เชื้อคำ

วัตถุประสงค์: เพื่อศึกษาผลของการให้ยาเฟนตานิลทางหลอดเลือดดำต่ออุบัติการณ์และความรุนแรงของการเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัว

วัสดุและวิธีการ: การศึกษาแบบสุ่มไปข้างหน้า ในผู้ป่วยเด็ก 144 ราย อายุระหว่าง 2-9 ปี โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มแรกให้เฟนตานิล 1 ไมโครกรัมต่อน้ำหนักตัวหนึ่งกิโลกรัม ทางหลอดเลือดดำ 15 นาที ก่อนเสร็จผ่าตัด กลุ่มที่สองให้น้ำเกลือ 0.9% ในปริมาณ 1 มิลลิลิตรต่อน้ำหนักตัว 10 กิโลกรัม ทำการประเมินภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัวโดยใช้ Watcha's behavioural emergence delirium scale

ผลการศึกษา: อุบัติการณ์การเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัวต่ำกว่าในกลุ่มที่ได้รับยาเฟนตานิลเมื่อเทียบกับกลุ่มควบคุม (11/72 vs. 23/72 ราย ตามลำดับ, $p = 0.03$) อย่างไรก็ตามพบว่าไม่มีนัยสำคัญทางสถิติในแง่ของความรุนแรงของการเกิดภาวะกระวนกระวายในผู้ป่วยทั้งสองกลุ่ม (1/72 vs. 6/72 ราย ตามลำดับ, $p = 0.12$) จำนวนของผู้ป่วยในกลุ่มที่ได้รับยาเฟนตานิลมีระดับความปวดแบบปานกลางและรุนแรงน้อยกว่าในกลุ่มควบคุม (16/72 vs. 30/72 ราย ตามลำดับ, $p = 0.02$) จำนวนผู้ป่วยที่ต้องการยาระงับปวดเสริมในกลุ่มที่ได้รับยาเฟนตานิลต่ำกว่ากลุ่มควบคุม (18/72 vs. 30/72 ราย ตามลำดับ, $p = 0.04$) ไม่มีความแตกต่างทางสถิติในแง่ของระยะเวลาฟื้นจากการดมสลบ ภาวะแทรกซ้อน และระยะเวลาที่อยู่ในห้องพักฟื้นระหว่างทั้งสองกลุ่มการศึกษา

สรุป: การให้ยาเฟนตานิลทางหลอดเลือดดำ 1 ไมโครกรัมต่อน้ำหนักตัวหนึ่งกิโลกรัม 15 นาที ก่อนเสร็จผ่าตัด ลดอุบัติการณ์การเกิดภาวะกระวนกระวายและความปวดหลังได้รับยาระงับความรู้สึกแบบทั้งตัว โดยไม่มีผลต่อการฟื้นจากการดมสลบช้าและภาวะแทรกซ้อนหลังผ่าตัด