RESEARCH ARTICLE

Effects of Fentanyl on Emergence Agitation in Children under Sevoflurane Anesthesia: Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and Objectives
The goal of this meta-analysis study was to assess the effects of fentanyl on emergence agitation (EA) under sevoflurane anesthesia in children.

Subjects and Methods
We searched electronic databases (PubMed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials) for articles published until December 2014. Randomized controlled trials (RCTs) that assessed the effects of fentanyl and placebo on EA under sevoflurane anesthesia in children that the outcome were the incidence of EA, postoperative pain, emergence time or adverse effects were included in this meta-analysis.

Results
A total of 16 studies, including 1362 patients (737 patients for the fentanyl group and 625 for the placebo group), were evaluated in final analysis. We found that administration of fentanyl decreased the incidences of EA (RR = 0.37, 95% CI 0.27~0.49, \( P < 0.00001 \)) and postoperative pain (RR = 0.59, 95% CI 0.41~0.85, \( P = 0.004 \)) but increased the incidence of postoperative nausea and vomiting (PONV) (RR = 2.23, 95% CI 1.33~3.77, \( P = 0.003 \)). The extubation time (WMD = 0.71 min, 95% CI 0.12~1.3, \( P = 0.02 \)), emergence time (WMD = 4.90 min, 95% CI 2.49~7.30, \( P < 0.0001 \)), and time in the postanesthesia care unit (PACU) (WMD = 2.65 min, 95% CI 0.76~4.53, \( P = 0.006 \)) were slightly increased. There were no significant differences in the time to discharge of day patients (WMD = 3.72 min, 95% CI -2.80~10.24, \( P = 0.26 \)).
Conclusion
Our meta-analysis suggests that fentanyl decreases the incidence of EA under sevoflurane anesthesia in children and postoperative pain, but has a higher incidence of PONV. Considering the inherent limitations of the included studies, more RCTs with extensive follow-up should be performed to validate our findings in the future.

Introduction
Emergence agitation (EA), is common that occurs during the early stage of recovery from general anesthesia in children, particularly in those under sevoflurane anesthesia [1]. Behavioral changes after general anesthesia in children have been described using different descriptive terms in different studies, such as ‘agitation’, ‘excitation’ and ‘delirium’. The definition of this condition has been described as ‘a mental disturbance during recovery from general anesthesia that may consist of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity and thrashing about in the bed’ [2]. Emergence delirium is an extreme form of EA which is described as ‘a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations’ and not all agitated children are truly delirious [3, 4]. We use the term ‘emergence agitation’ to encompass this clinical entity for the purpose of this meta-analysis.

EA was first described in the early 1960s [3]. Depending on the definition and evaluation methods adopted, the prevalence of EA is between 2% and 80% [5], and it is more common in preschool children. EA is attributed to many factors, such as age, rapid awakening after surgery, pain, anxiety before anesthesia, type of surgery, individuality of children, and anesthetics used. Pain and EA can overlap and it is difficult to distinguish the two phenomenon [6]. Although EA is generally self-limited, it can be severe and may result in physical harm to the child, the need for further post-anesthesia care and eventually supplemental sedative or analgesic drugs [7, 8]. Also, an unsettle behaviour reduces parental and caregivers’ satisfaction. Long-term psychological implications of early postoperative negative behavior are still unclear, but the new-onset postoperative maladaptive behavioral changes including separation anxiety, apathy and withdrawal, eating problems, and sleep problems are closely associated with EA [9].

Different strategies have been suggested for decreasing the incidence and severity of EA, such as the administration of sedative medication before induction and changes in the anesthesia maintenance technique [5, 10, 11]. Drugs such as fentanyl may reduce the incidence of EA under sevoflurane anesthesia. Fentanyl is a potent opioid receptor agonist with sedative and analgesic effects. It is routinely used in the practice of pediatric perioperative medicine. Some clinical trials have shown that fentanyl can prevent EA under sevoflurane anesthesia in children [12, 13]. However, no meta-analysis based on the available randomized trials in the literature has been conducted. Therefore, we conducted a systematic review to compare the effect of fentanyl and placebo on emergence agitation in children under sevoflurane anesthesia.

Methods
The prospective protocol, literature searching strategies, inclusion and exclusion criteria, outcome measurements, and statistical analysis methods used were based on the recommendations of the PRISMA statement and the Cochrane Collaboration for systematic reviews and meta-analysis [14, 15].
Literature search strategy
A comprehensive literature search was performed in December 2014. We searched electronic databases, including PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trial. The key search terms were as follows: sevoflurane, emergence agitation/excit, delirium/confusion, (postoperative/postanesthetic) (agitation/confusion/behavioral change), children/infant, and fentanyl. The manual searching of the references of the retrieved studies were used to extend the search. Only English articles were considered. When necessary, we contacted the authors for additional unpublished data.

Inclusion and exclusion criteria
RCTs comparing fentanyl with placebo (normal saline) administered perioperatively to reduce EA incidence in pediatric patients (aged 1–14 years) with sevoflurane anesthesia were included in this systematic review. We excluded letters to the editor, editorials, case reports, reviews, and animal studies.

Data extraction and outcome measurements
Two independent authors extracted and summarized data from eligible trials. Disagreements were resolved by discussion with other authors. We extracted the following data from each eligible trial: first author, publication year, patient ages, type of surgery, number of patients, sedative premedication, dose, timing, and route of administration of fentanyl/placebo, sevoflurane anesthesia protocol, perioperative analgesia, the EA incidence, postoperative pain, emergence time, extubation time, time in postanesthesia care unit (PACU), time to discharge and adverse events.

The primary outcome is the incidence of emergence agitation (EA). EA incidence was defined as the incidence of participants with postoperative behavioural disturbance during emergence from anesthesia, which was measured by the authors of included studies. The secondary outcomes examined in this study included pain incidence in PACU, extubation time, emergence time, time in the PACU, the time to discharge of day patients and adverse events, such as the incidence of PONV, respiratory adverse events and haemodynamic changes requiring intervention. Pain incidence in PACU was defined by the authors of the studies using the Objective Pain Scale (OPS), Children’s and Infant’s Postoperative Pain Scale (CHIPPS) or four-point Verbal Rating Scale. Extubation time was defined as the time interval from anesthetic discontinuation to extubation. Emergence time was measured as the time between discontinuation of anesthesia and spontaneous eye opening. Time in the PACU was defined as the time interval from anesthetic discontinuation to discharge from the PACU. The time to discharge of day patients was defined as the time between anesthetic discontinuation and discharge from the hospital of day patients. The incidence of PONV was assessed by evaluating nausea and vomiting behaviors from the entrance of patients into the PACU to 24 h after surgery.

Quality assessment and statistical analysis
We examined the quality of studies included in the meta-analysis using the Cochrane Collaboration’s tool for assessing risk of bias [16]. The domains included a random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

Meta-analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata software, version 12.0 (Stata Corporation, College Station, TX). Relative risks (RRs) and weighted mean differences (WMDs) were used to compare dichotomous and continuous variables, respectively, both with corresponding 95% confidence intervals (CIs).
confidence interval for an RR of <1 indicated that the incidence of the test target in the fentanyl group was lower than that in the placebo group. If studies presented continuous data as median and range values, the means and standard deviations were transformed as described by Hozo et al.\cite{17}

Statistical heterogeneity was assessed using the chi-square test with a significance of $P<0.10$ \cite{18}. Heterogeneity was quantified with the $I^2$ statistic \cite{19}. If $P>0.10$ and $I^2<50\%$, fixed effects analysis was conducted to calculate the pooled OR; otherwise, a random effects model was used \cite{16}. We conducted subgroup analyses to investigate possible causes of heterogeneity. Sensitivity analyses were performed by removing each trial individually to evaluate the quality and consistency of the results. To evaluate whether potential publication bias might have affected statistical results, we applied funnel plots, Begg’s test and Egger’s test. All statistical tests were 2-sided.

Results

Evidence synthesis

Our initial search yielded 306 studies. After removing 156 duplicate studies, we evaluated the abstracts of 150 studies. From this evaluation, 94 studies were excluded as unrelated, 1 was excluded as editorial, 5 were excluded as letters, 7 were excluded as reviews, and 3 were excluded as case reports. The full-text review of 40 studies led to the exclusion of 24 for the following reasons: 13 for the lack of a control group \cite{20–31}, 1 for being older than 14 years \cite{32}, 3 for the lack of availability of a full-text version \cite{33–35} and 7 for not being written in English \cite{36–42}. Therefore, 16 studies \cite{4, 12, 43–56}, including 1362 cases (737 cases for the fentanyl group and 625 cases for the placebo group), reached the predefined inclusion criteria and were finally included in our analysis (Fig 1).

Characteristics of eligible studies

The characteristics of the included studies are shown in Table 1. Among these studies, two different fentanyl doses were introduced in 3 trials \cite{12, 48, 53}. For the trials that compared a control group with multiple intervention groups using different fentanyl doses, we combined the intervention groups to conduct a single pair-wise comparison. Single fentanyl administration was performed in 15 trials \cite{4, 12, 43–47, 49–56}, and continuous infusion was carried out in 1 trial \cite{48}. Five studies were performed in the USA \cite{12, 46, 53–55}, three in Egypt \cite{43, 47, 56}, two each in Korea \cite{44, 49} and Turkey \cite{50, 52}, and one each in Italy \cite{4}, China \cite{45}, Japan \cite{48} and Saudi Arabia \cite{51}.

Primary outcomes

EA incidence. Sixteen studies \cite{4, 12, 43–56} (n = 1362) reported the incidence of EA and were included in pooled analysis of fentanyl vs. placebo (Fig 2). There was strong evidence that fentanyl significantly reduced the incidence of EA in children with sevoflurane anesthesia (RR = 0.37, 95% CI 0.27–0.49, $P<0.00001$, $I^2 = 49\%$) (Table 2).

We conducted subgroup analysis separately because confounding factors, such as premedication, type of surgery, preschool-aged children and pain, may have affected the incidence of EA (Table 3). Subgroup analysis of the timing of administration revealed that the use of fentanyl both before and at the end of surgery resulted in a preventive effect against EA (RR = 0.39, 95% CI 0.28–0.54, $P<0.00001$, $I^2 = 59\%$; RR = 0.26, 95% CI 0.15–0.47, $P<0.00001$, $I^2 = 0\%$). Analysis of 12 intravenous fentanyl trials showed that this intervention was effective (RR = 0.35, 95% CI 0.24–0.50, $P<0.00001$, $I^2 = 53\%$). Three intranasal studies of this drug had
RR of 0.30 (95% CI 0.12–0.72, \( P = 0.008, I^2 = 50\% \)), and one oral study had an RR of 0.54 (95% CI 0.35–0.83, \( P = 0.005 \)). The effect of midazolam is still an ongoing debate. The meta-analysis by Zhang et al found midazolam had a significant effect on preventing EA [57] while the meta-analysis by Dahmiani et al found midazolam to be ineffective for the prevention of EA. On the contrary, midazolam might even trigger EA [5]. To eliminate the effects of this drug, we performed subgroup analysis, including 9 trials without premedication and 4 studies with midazolam premedication, and showed the prevention of EA in the fentanyl group (RR = 0.34, 95% CI 0.23–0.50, \( P < 0.0001, I^2 = 55\% \); and RR = 0.34, 95% CI 0.13–0.90, \( P = 0.03, I^2 = 63\% \), respectively). Ear, nose and throat (ENT) procedures were reported to be independent risk factors for EA [58]. The protocols of 8 studies included ENT procedure for children. The pooled RR of ENT procedure studies was 0.45 (95% CI 0.32–0.64, \( P < 0.0001, I^2 = 33\% \)). When pooled analysis was limited to studies of patients who underwent minor urologic or inguinal surgery and received an appropriate regional block with enough local anesthetics, we found that the pooled
| Author year | Age         | Surgery                          | Study/ control | Study intervention                        | Premedication                              | Analgesics                               | Regional block                  | Assessment methods of EA |
|-------------|-------------|----------------------------------|----------------|-------------------------------------------|--------------------------------------------|------------------------------------------|----------------------------------|--------------------------|
| Borton 2014 | 2-11yr      | subumbilical surgery             | 29/29          | Fentanyl 2ug/kg iv before surgery         | midazolam 0.5mg/kg(Oral)                   | Acetaminophen 40mg/kg                   | ilio-inguinal/iliohypogastric block or Penile block or caudal block | ED:PAED > 12, EA:Cravero score ≥4 |
| Rashad 2014 | 1-3 yr      | Ambulatory hypospadas repair     | 20/20          | Fentanyl 1ug/kg iv before the end of surgery | No                                         | No                                       | Caudal block                   | Cravero Scale ≥4           |
| Kim 2013    | 1.5-6yr     | Ambulatoryingual hernia repair   | 66/70          | Fentanyl 1ug/kg iv before the end of surgery | No                                         | No                                       | Caudal block                   | Aono's scale ≥3 or Cravero scale ≥4 |
| Li 2011     | 3-11yr      | Adenotonsillectomy              | 34/34          | Fentanyl 2ug/kg iv after induction         | No                                         | Tramadol 2 mg/kg and dexamethasone 0.1 mg/kg | No                                 | Aono's scale ≥3           |
| Pestieau 2011 | 0.5-6yr    | BMT                              | 23/27          | Fentanyl 2ug/kg intranasal after induction | No                                         | No                                       | No                               | Watcha scale ≥2            |
| Asaad 2011  | 5-10yr      | Inguinal hernia repair, hydrocele, or circumcision | 28/30          | Fentanyl 1ug/kg iv after intubation        | No                                         | No                                       | Caudal block                   | Aono's scale ≥3           |
| Inomata 2010 | 2-6yr       | Minor surface surgery           | 93/46          | Fentanyl1 ug/kg (2ug/kg) iv and continuous infusion 0.5ug/kg/h(1ug/kg/h) before intubation | No                                         | No                                       | Field block                    | PAED > 10                 |
| Jung 2010   | 3-10 yr     | Stabismus entail surgery         | 49/44          | Fentanyl 1.5ug/kg iv after induction       | No                                         | Ketorolac 0.5mg/kgOndansetron 0.1 mg/kg | No                                | Cohen scale = 3            |
| Erdil 2009  | 2-7yr       | Adenoidectomy with or without BMT | 30/30          | Fentanyl2 ug/kg iv after induction         | Paracetamol 40mg/kg (rectally)             | Dexamethasone 0.5mg/kg                  | No                               | 5-point scale ≥4           |
| Makharita 2009 | 3-8yr       | BMT                              | 40/40          | Fentanyl 1ug/kg iv after the end of surgery | Acetaminophen 40mg/kg (rectally)           | No                                       | No                               | Aono’s ≥3                   |
| Bakhamess2009 | 2-6yr       | Adenotonsillectomy with or without BMT | 40/40          | Fentanyl 1.5ug/kg iv after intubation      | midazolam 0.5mg/kg(Oral)                   | Paracetamol 40mg/kg rectal              | No                               | 10-point scale ≥2          |
| Demirbilek2004 | 2-7yr       | Adenoidectomy or tonsillectomy or both | 30/30          | Fentanyl 2.5ug/kg iv after induction       | Midazolam 0.5mg/kg orally                  | Acetaminophen 30mg/kg rectal            | No                               | Cohen scale = 3            |
| Binstock2004 | 2-10yr      | Outpatient procedure             | 74/51          | OTFC10-15ug/kg (100ug) before induction    | OTFC10-15ug/kg (100ug/kg) vs. No          | Bupivacaine 0.125%, 1ml/kg caudal block | Bupivacaine 0.125%, 1ml/kg Caudal block | Anxiety/ agitation ≥2       |
| Cravero 2003 | 1.5-10yr    | MRI scanning                     | 16/16          | Fentanyl 1ug/kg iv before end of surgery   | No                                         | No                                       | No                               | Cravero scale ≥4           |
| Finkel 2001 | 0.5-5yr     | BMT                              | 101/49         | Fentanyl 1ug/kg(2ug/kg) intranasal after induction | No                                         | Acetaminophen 40mg/kg (rectally)       | No                               | Watcha scale ≥3            |
| Galinkin 2000 | 0.75-6yr    | BMT                              | 64/69          | Fentanyl 2ug/kg intranasal after induction | Acetaminophen1 0mg/kg, midazolam 0.5 mg/kg orally | No                                     | No                               | Aono’s scale ≥3           |

BMT = bilateral myringotomy and tubes, MRI = magnetic resonance imaging, ND = not determined, PACU = post anesthesia care unit; Oral transmucosal fentanyl citrate = OTFC

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RR was 0.34 (95% CI 0.21–0.57, \(P<0.0001\), \(I^2=0\%\)). Seven trials evaluated EA in preschool children younger than 7 years of age. We found that the pooled RR was 0.33 (95% CI 0.21–0.52, \(P<0.00001\)) but that the \(I^2\) remained high at 59%.

### Secondary outcomes

#### Pain incidence in PACU

Five studies [4, 46, 50, 52, 56] (n = 308) were included in pooled analysis of pain incidence in the PACU between the fentanyl and placebo group. The data were homogeneous (\(I^2=0\%\), \(P=0.65\)), and the pooled results suggested that fentanyl significantly decreased the incidence of pain in children in the PACU (RR = 0.59, 95%CI 0.41–0.85, \(P=0.004\)) (Fig 3).

#### Extubation time

A total of 5 studies [45, 48–50, 52] reported extubation time in children with sevoflurane anesthesia, and the combined data suggested that it was prolonged by fentanyl (WMD = 0.71 min, 95% CI 0.12–1.30, \(P=0.02\)). There was no heterogeneity among the results (\(F=0\%\), \(P=0.79\)) (Fig 4).

#### Emergence time

Emergence time was examined in eight studies [4, 43, 44, 46, 47, 50, 52, 53]. We found that the emergence time in the fentanyl group was longer than that in the control group (WMD = 4.90 min, 95%CI 2.49–7.30, \(P<0.0001\)) (Fig 5). The test for heterogeneity

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**Table:**

| Study or Subgroup | Fentanyl | Placebo | Risk Ratio | Risk Ratio |
|------------------|----------|---------|------------|------------|
|                  | Events   | Total   | Total      | Weight     | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Asaad 2011       | 6        | 28      | 12         | 30         | 6.8% | 0.54 [0.23, 1.23] |
| Bakhamees 2009   | 14       | 40      | 21         | 40         | 10.4% | 0.67 [0.40, 1.12] |
| Binstock 2004    | 22       | 74      | 28         | 51         | 11.8% | 0.54 [0.35, 0.83] |
| Bortone 2014     | 3        | 29      | 12         | 29         | 4.5%  | 0.25 [0.08, 0.79] |
| Craver 2003      | 2        | 16      | 9          | 16         | 3.5%  | 0.22 [0.06, 0.87] |
| Demirbilek 2004  | 2        | 30      | 4          | 30         | 2.7%  | 0.50 [0.10, 2.53] |
| Erdil 2009       | 4        | 30      | 14         | 30         | 5.6%  | 0.29 [0.11, 0.77] |
| Finkel 2001      | 19       | 101     | 21         | 49         | 10.4% | 0.44 [0.26, 0.74] |
| Galinkin 2000    | 1        | 64      | 16         | 69         | 1.9%  | 0.07 [0.01, 0.49] |
| Inomata 2010     | 16       | 93      | 37         | 46         | 11.1% | 0.21 [0.13, 0.34] |
| Jung 2010        | 1        | 49      | 16         | 44         | 1.9%  | 0.06 [0.01, 0.41] |
| Kim 2013         | 5        | 66      | 19         | 70         | 6.0%  | 0.28 [0.11, 0.70] |
| Li 2011          | 15       | 34      | 24         | 34         | 11.5% | 0.63 [0.40, 0.97] |
| Makharita 2009   | 3        | 40      | 11         | 40         | 4.3%  | 0.27 [0.08, 0.90] |
| Pestieau 2011    | 3        | 23      | 11         | 27         | 4.5%  | 0.32 [0.10, 1.01] |
| Rashad 2014      | 2        | 20      | 8          | 20         | 3.3%  | 0.25 [0.06, 1.03] |
| **Total (95% CI)** | 737     | 625     | **100.0%** | 0.37 [0.27, 0.49] |

**Fig 2. Forest plot and meta-analysis of EA incidence.** EA = emergence agitation; M-H = Mantel-Haenszel method; CI = confidence interval.

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revealed an $I^2$ value of 95% ($P<0.00001$). When we removed the studies of Erdil 2009 [50], Kim 2013 [44], and Rashad 2014 [43], the heterogeneity was significantly decreased ($I^2 = 14\%$, $P = 0.33$), and the pooled WMD was 1.04 min (95% CI 0.81~1.27, $P<0.00001$).

**Time in PACU.** Time in the PACU was examined in 13 studies [4, 12, 43–48, 51–53, 55, 56]. The time in the PACU in the fentanyl group was longer than that in the control group (WMD = 2.65 min, 95% CI 0.76–4.53, $P = 0.006$). Because the $I^2$ value was 79% ($P<0.00001$), the random effects model was used to pool the data (Fig 6).

**Time to discharge (day patients).** The time to discharge of day patients was explored in 5 trials [12, 51, 54–56], and the data were homogeneous ($I^2 = 41\%$, $P = 0.15$). The pooled data suggested that no evidence of a difference in time to discharge (WMD = 3.72 min, 95% CI -2.80–10.24, $P = 0.26$) between the fentanyl and placebo groups (Fig 7).

**Adverse events.** The assessment of 9 studies [4, 12, 43, 44, 50, 52, 53, 55, 56] together showed that PONV occurred in 103 of 454 patients in the fentanyl group and 42 of 388 patients in the placebo group. The pooled results showed that fentanyl significantly increased the PONV incidence in the children under sevoflurane anesthesia (RR = 2.23, 95% CI 1.33–3.77, $P=0.003$).

### Table 2. Meta-analysis results of all items.

| Items               | No. of studies | No. of participants | Effect size (95%CI) | $P$-value | $I^2$,% | Heterogeneity $P$-value |
|---------------------|----------------|---------------------|---------------------|-----------|---------|------------------------|
| EA                  | 16             | 1362                | RR 0.37(0.27,0.49)  | <0.00001  | 49      | 0.01                   |
| Pain                | 5              | 308                 | RR 0.59(0.41,0.85)  | 0.004     | 0       | 0.65                   |
| Extubation time, min| 5              | 420                 | WMD 0.71(0.12,1.3)  | 0.02      | 0       | 0.79                   |
| Emergence time, min | 8              | 587                 | WMD 4.9(2.49,7.3)   | <0.0001   | 95      | <0.00001               |
| Time of PACU, min   | 13             | 1175                | WMD 2.65(0.76,4.53) | 0.006     | 79      | <0.00001               |
| Time to discharge, min | 5           | 475                 | WMD 3.72(2.80,10.24)| 0.26      | 41      | 0.15                   |
| PONV                | 9              | 842                 | RR 2.23(1.33,3.77)  | 0.003     | 42      | 0.09                   |

RR = relative risk; WMD = weighted mean difference; CI = confidence interval; EA = emergence agitation; PONV = postoperative nausea and vomiting; PACU = post anesthesia care unit.

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### Table 3. Effects of Subgroup Analysis on Meta-analysis Comparing fentanyl and placebo.

| Subgroup                  | No. of studies | No. of participants | RR (95%CI) | $P$-value | $I^2$,% | Heterogeneity $P$-value |
|---------------------------|----------------|---------------------|------------|-----------|---------|------------------------|
| Timing of administration  |                |                     |            |           |         |                        |
| Before surgery            | 12             | 1074                | 0.39[0.28,0.54] | <0.00001 | 59      | 0.005                  |
| before the end of surgery | 4              | 288                 | 0.26[0.15,0.47] | <0.00001 | 0       | 0.99                   |
| Route of administration   |                |                     |            |           |         |                        |
| Intravenous               | 12             | 904                 | 0.35[0.24,0.50] | <0.00001 | 53      | 0.01                   |
| Intranasal                | 3              | 333                 | 0.30[0.12,0.72] | 0.008     | 50      | 0.14                   |
| Oral                      | 1              | 125                 | 0.54[0.35,0.83] | 0.005     | NA      | NA                     |
| Premedication             |                |                     |            |           |         |                        |
| without                   | 9              | 766                 | 0.34[0.23,0.50] | <0.00001 | 55      | 0.02                   |
| with midazolam            | 4              | 331                 | 0.34[0.13,0.90] | 0.03      | 63      | 0.05                   |
| Surgery                   |                |                     |            |           |         |                        |
| ENT                       | 8              | 681                 | 0.45[0.32,0.64] | <0.0001   | 33      | 0.16                   |
| subumbilical              | 4              | 292                 | 0.34[0.21,0.57] | <0.0001   | 0       | 0.61                   |
| Preschool children(aged<7 yr) | 7         | 728                 | 0.33[0.21,0.52] | <0.00001 | 59      | 0.02                   |

NA = not applicable; OR = odds ratio; CI = confidence interval; Ear, nose and throat = ENT.

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One study [44] reported that a participant experienced suspicious laryngospasm, and 4(6%) patients had airway obstruction in the fentanyl group. Another study [53] showed that the risk of drug-related respiratory adverse events was higher for patients receiving oral transmucosal fentanyl citrate (OTFC) than for other patients; however, most of the adverse events were mild. No study reported hemodynamic events requiring intervention in any arm.

Methodological qualities of included studies and potential sources of bias

The methodological qualities of the included trials were showed in Table 4. No study was found to beat a high risk of bias for any of the criteria considered. The blinding of participants and personnel, the blinding of the outcome assessment, the presence of incomplete outcome
Fig 5. Forest plot and meta-analysis of emergence time. EA = emergence agitation; M-H = Mantel-Haenszel method; CI = confidence interval.

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Fig 6. Forest plot and meta-analysis of time in PACU. EA = emergence agitation; M-H = Mantel-Haenszel method; CI = confidence interval; PACU = Postanesthesia care unit.

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data, and selective reporting were determined to be at a low risk of bias in all included studies. Random sequence generation was unclear in five trials [45, 47, 49, 51, 53], and allocation concealment was unclear in 14 studies [4, 12, 43, 44, 46, 48–55].

A funnel plot of the included studies that reported the incidence of EA showed potential publication bias (Begg’s test, \( P = 0.022 \), Egger’s test, \( P = 0.023 \)) (Fig 9). Considering the effect of the missing trials, we conducted a trim-and-fill analysis and the analysis showed “no trimming performed; data unchanged”.

Fig 7. Forest plot and meta-analysis of time to discharge. EA = emergence agitation; M-H = Mantel-Haenszel method; CI = confidence interval.

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Fig 8. Forest plot and meta-analysis of PONV incidence. EA = emergence agitation; M-H = Mantel-Haenszel method; CI = confidence interval; PONV = postoperative nausea and vomiting.

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Discussion

This systematic review and meta-analysis of 16 RCTs, including 1362 patients, indicates that fentanyl significantly reduces the incidence of EA under sevoflurane anesthesia in children and decreases postoperative pain but it increases the incidence of PONV. The extubation time, emergence time, and time in the PACU were slightly prolonged. We found no significant difference in the time to discharge of day patients.

Several previous meta-analyses indicate that fentanyl can reduce the incidence of EA under sevoflurane anesthesia in children [59], whereas the meta-analysis by Dahmiani et al state that intravenous fentanyl failed to prevent EA [5]. In our subgroup analysis, we found that both intravenous and intranasal fentanyl showed to be effective. The reasons for these conflicting results may be due to inclusion of only two studies in the meta-analysis by Dahmiani et al.

Fentanyl, a short-acting opioid analgesic, is used to reduce the incidence of pain. Some investigators have argued that pain experienced during impaired consciousness in children results in severe EA [13, 58, 60]. Our findings also showed that fentanyl decreased the incidence of pain in children in the PACU (RR = 0.59, 95%CI 0.41~0.85, P = 0.004) and reduced the incidence of EA (RR = 0.37, 95% CI 0.27~0.49, $P<0.00001$, $I^2 = 0\%$) in children under sevoflurane anesthesia. However, it was still difficult to fully identify EA or pain-induced behavioral disorders in the children evaluated in the present study. Locatelli et al suggested that the splitting of PAED scale into ED1 and ED2 scores might help to separate ED from pain [61]. In addition, previous studies have reported a frequent incidence of EA in patients who have received sevoflurane for genitourinary surgery with an adequate caudal block and for non painful interventions, such as magnetic resonance imaging [7, 54]. Following restriction of the studies achieving a high level of pain relief during surgery by regional nerve block, the preventative effect of fentanyl remained significant (RR = 0.34, 95% CI 0.21~0.57, $P<0.00001$, $I^2 = 0\%$).
Thus, it is hard to establish an explicit relationship between pain and EA, and pain may not be the only factor affecting the occurrence of EA in children. Fentanyl is effective for EA in a rather unspecific way. Whatever the reason for EA might be pain, delirium, agitation for other reasons such as parental separation, hunger, thirst etc, fentanyl provides analgesia and sedation and hence disrupts agitation and crying. It resolves the problem even without knowing the exact underlying cause, especially in those situations where there might be an overlap between pain and delirium.

Some studies have demonstrated that rapid awakening is one of the factors contributing to EA [62] because of the low blood-gas solubility and rapid emergence characteristics of sevoflurane. In the current study, the children administered fentanyl were found to have a slightly prolonged extubation time (WMD = 0.71 min, 95% CI 0.12~1.3, $P = 0.02$, $I^2 = 0\%$), emergence time (WMD = 4.90 min, 95% CI 2.49~7.30, $P<0.0001$, $I^2 = 95\%$) and time in the PACU (WMD = 2.65 min, 95% CI 0.76~4.53, $P = 0.006$) and a lower incidence of EA. Some authors have found that the incidence of EA is not reduced by delayed emergence from sevoflurane anesthesia in children [63]. Therefore, it is still difficult to confirm that fentanyl reduces the incidence of EA by preventing rapid emergence from sevoflurane anesthesia.

The incidence of PONV was significantly higher in the fentanyl group than the placebo group (RR = 2.23, 95% CI 1.33~3.77, $P = 0.003$, $I^2 = 42\%$). However, a lack of postoperative follow-up after more than 24 hours may have been a limiting factor in the interpretation of these study results. Other adverse events were reported in two studies; however, we did not find any

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**Fig 9. Funnel plots illustrating meta-analysis EA incidence.** SE = standard error; RR = Relative risk; EA = emergence agitation.

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serious adverse events in any of the included trials. Additional adverse events were infrequent in most studies mentioning 'no adverse events' and in those not addressing them at all. Thus, we were notable to ascertain safety.

Between-study heterogeneity was significant for some of the continuous variables but was not significant for the dichotomous outcomes. Different surgery types, children's ages, premedication, timing and the route of administration were described in the included studies. These differences may have resulted in the significant between-study heterogeneity. The effect of heterogeneity may have been reduced by using the random effects model, but not abolished.

Some limitations need to be considered for the present study. The main limitation is that the incidence of EA may have been greatly influenced by the use of different scales with different cut-off values to define the presence of EA and some of the scales are not validated [64]. Because small children cannot verbalize pain, anxiety, thirst or hunger, it is difficult to interpret their behaviors [65]. Although some studies used a reliable pain scale and the PAED scale to decrease errors associated with pain, a clear differentiation between EA and agitation because of pain could not be guaranteed. Future systematic reviews should explore different EA assessment tools separately when a sufficient amount of data is available. In addition, the follow-up time was generally short; therefore, any impacts on the long-term outcome of EA remain to be validated. Furthermore, we restricted the study selection to the English language and unpublished studies were not included in this meta-analysis adding a language bias and publication bias. Some studies reported that the exclusion of non-English studies may result in more conservative estimates of treatment effects, because studies with positive results were more likely to be published and more likely to be published in English [66]. Nevertheless, we searched for studies with multiple strategies, included and evaluated the methodological qualities of the studies with strict criteria, and minimized heterogeneity with subgroup analysis. Therefore, we provide the up-to-date information on this topic.

Conclusions
In conclusion, this systematic review and meta-analysis indicates that fentanyl may be associated with a decreased incidence of EA in children under sevoflurane anesthesia in addition to reduced postoperative pain, but has a higher incidence of PONV. However, considering the inherent limitations of the included studies, more RCTs with extensive follow-up should be performed to validate our findings in the future.

Supporting Information
S1 Checklist. PRISMA Checklist. (DOC)
S1 File. A list of full-text excluded articles. (DOCX)

Author Contributions
Conceived and designed the experiments: FMS XQH. Performed the experiments: FMS YX. Analyzed the data: FMS YX WX. Contributed reagents/materials/analysis tools: FMS WX QZ. Wrote the paper: FMS YX WX PY.

References
1. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth. [Clinical Trial; Comparative
1. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology. [Journal Article; Validation Studies]. 2004 2004-05-01; 100(5):1138–45. PMID: 15114210
2. ECKENHOFF JE, KNEALE DH, DRIPPS RD. The incidence and etiology of postanesthetic excitement. A clinical survey. Anesthesiology. [Journal Article]. 1961 1961-09-01; 22:667–73. PMID: 1389092
3. Kuratani N, Oi Y. Greater incidence of emergence agitation in children after sevoflurane anesthesia as compared with halothane: a meta-analysis of randomized controlled trials. Anesthesiology. [Journal Article; Meta-Analysis; Review]. 2008 2008-08-01; 109(2):225–32. doi: 10.1097/ALN.0b013e1817f5c18 PMID: 18648231
4. Finkel JC, Cohen IT, Hannallah RS, Fawley G, Somaini M, Engelhardt T, Ingelmo PM. The effect of fentanyl and clonidine on early postoperative negative behavior in children: a double-blind placebo controlled trial. Paediatr Anaesth. [Journal Article; Research Support, Non-U.S. Gov't]. 2014 2014-06-01; 24(6):614–9. doi: 10.1111/pa.12388 PMID: 24666767
5. Dahmani S, Stany I, Brasier C, Lejeune C, Bruneau B, Wood C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth. [Journal Article; Meta-Analysis; Review]. 2010 2010-02-01; 104(2):216–23. doi: 10.1093/bja/aep376 PMID: 20047899
6. Somaini M, Sahillioglu E, Marzaroli C, Lovisari F, Engelhardt T, Ingelmo PM. Emergence delirium, pain or both? a challenge for clinicians. Paediatr Anaesth. [Journal Article]. 2015 2015-05-01; 25(5):524–9. doi: 10.1111/pa.12580 PMID: 25580984
7. Veyckemans F. Excitation phenomena during sevoflurane anaesthesia in children. Curr Opin Anaesthesiol. [Journal Article]. 2001 2001-06-01; 14(3):339–43. PMID: 17019113
8. Kuratani N, Oi Y. Greater incidence of emergence agitation in children after sevoflurane anesthesia as compared with halothane: a meta-analysis of randomized controlled trials. Anesthesiology. [Journal Article; Meta-Analysis; Review]. 2008 2008-08-01; 109(2):225–32. doi: 10.1097/ALN.0b013e1817f5c18 PMID: 18648231
9. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. [Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.]. 2004 2004-12-01; 99(6):1648–54. PMID: 15620408
10. Aouad MT, Yazbeck-Karam VG, Nasr VG, El-Khatib MF, Kanazi GE, Bleik JH. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. Anesthesiology. [Journal Article; Research Support, Non-U.S. Gov't]. 2007 2007-11-01; 107(5):733–8. PMID: 18073548
11. Zhang C, Hu J, Liu X, Yan J. Effects of intravenous dexmedetomidine on emergence agitation in children under sevoflurane anesthesia: a meta-analysis of randomized controlled trials. PLoS One. [Journal Article; Meta-Analysis]. 2014 2014-01-20; 9(6):e99718. doi:10.1371/journal.pone.0099718 PMID: 24932765
12. Finke JC, Cohen IT, Finkel JC, Hannallah RS, Patel KM, Kim MS, Hummer KA, et al. The effect of intranasal fentanyl on the emergence characteristics after sevoflurane anesthesia in children undergoing surgery for bilateral myringotomy tube placement. Anesth Analg. [Clinical Trial; Journal Article; Randomized Controlled Trial]. 2001 2001-05-01; 92(5):1164–8. PMID: 11233340
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. [Consensus Development Conference; Guideline; Journal Article; Meta-Analysis; Review]. 2014 2014-01-20; 9(6):e99718. doi: 10.1371/journal.pmed.1000100 PMID: 24932765
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. [Guideline; Journal Article; Research Support, Non-U.S. Gov't]. 2009 2009-08-18; 18(4):264–9. W64. PMID: 19622511
15. Higgins J GS. Cochrane handbook for systematic reviews of interventions. New York, NY: Cochrane Collaboration, John Wiley and Sons; 2008.
16. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. [Journal Article]. 2005 2005-01-20; 5:13. PMID: 15840177
17. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. Psychol Methods. [Journal Article]. 2001 2001-09-01; 6(3):203–17. PMID: 11570228
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. [Journal Article; Research Support, Non-U.S. Gov't]. 2002 2002-06-15; 21(11):1539–58. PMID: 12111919
20. Li X, Zhang Y, Zhou M, Xia Q, Li W, Lu Q. The effect of small dose sufentanil on emergence agitation in preschool children following sevoflurane anesthesia for elective repair of unilateral inguinal hernia. Saudi Med J. [Journal Article; Randomized Controlled Trial]. 2013 2013-01-01; 34(1):40–5. PMID: 23299158

21. Hippard HK, Govindan K, Friedman EM, Sulek M, Giannoni C, Larrier D, et al. Postoperative analgesic and behavioral effects of intranasal fentanyl, intravenous morphine, and intramuscular morphine in pediatric patients undergoing bilateral myringotomy and placement of ventilating tubes. Anesth Analg. [Comparative Study; Journal Article; Randomized Controlled Trial]. 2012 2012-08-01; 115(2):356–63. doi: 10.1213/ANE.0b013e31825afe3 PMID: 22669347

22. GUAN L, WANG R, LI Q. Clinical observation of applying sufentanil in pediatric neuroanesthesia. The Journal of Clinical Anesthesiology. 2011; 27(1004-5805(2011)7<644:SFTNYZQ>2.0.TX;2-H7):644–6.

23. Rampersad S, Jimenez N, Bradford H, Seidel K, Lynn A. Two-agent analgesia versus acetaminophen in children having bilateral myringotomies and tubes surgery. Paediatr Anaesth. [Comparative Study; Journal Article; Randomized Controlled Trial]. 2010 2010-11-01; 20(11):1028–35. doi: 10.1111/j.1460-9592.2010.03427.x PMID: 20964769

24. Patel A, Davidson M, Tran MC, Quraishi H, Schoenberg C, Sant M, et al. Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy. Anesth Analg. [Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2010 2010-10-01; 111(4):1004–10. PMID: 20705788

25. Patel A, Davidson M, Tran MCJ, Quraishy H, Schoenberg C, Sant M, et al. Dexmedetomidine Infusion for Analgesia and Prevention of Emergence Agitation in Children with Obstructive Sleep Apnea Syndrome Undergoing Tonsillectomy and Adenoidectomy. Anesth Analg. 2010; 111(4):1004–10. PMID: 20705788

26. Shen X, Li W. Pharmacodynamics of fentanyl for inhibition of emergence agitation after sevoflurane-remfentanil anesthesia in children. Chinese Journal of Anesthesiology. 2010; 30(0254-1416(2010)30:3<303:FTNYZQ>2.0.TX;2-D3):303–5.

27. M SM, SM A. Oral midazolam with low dose ketamine, fentanyl, or ketoprofen for the prevention of emergence agitation after pediatric ambulatory surgery. Egyptian Journal of Anaesthesia. 2008(1: ).

28. Kim CH, Jo HY, Han JY, Kim DY. The Effect of Fentanyl and Remifentanil on the Side Effect after Sevoflurane Anesthesia in Children undergoing Herniorrhaphy. Korean Journal of Anesthesiology. 2007; 53 (5):609–14.

29. Aouad MT, Kanazi GE, Siddik-Sayyid SM, Gerges FJ, Rizk LB, Baraka AS. Preoperative caudal block prevents emergence agitation in children following sevoflurane anesthesia. Acta Anaesthesiol Scand. [Clinical Trial; Journal Article; Randomized Controlled Trial]. 2005 2005-03-01; 49(3):300–4. PMID: 15752392

30. Cohen IT, Finkel JC, Hannonah RS, Hummer KA, Patel KM. The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. Anesth Analg. [Clinical Trial; Journal Article; Randomized Controlled Trial]. 2002 2002-05-01; 94(5):1178–81. PMID: 11973185

31. Abdelhalim AA, Alarfaj AM. The effect of ketamine versus fentanyl on the incidence of emergence agitation after sevoflurane anesthesia in pediatric patients undergoing tonsillectomy with or without adenoidectomy. Saudi J Anaesth. [Journal Article]. 2013 2013-10-01; 7(4):392–8. doi: 10.4103/1658-354X.121047 PMID: 24348289

32. Hung WT, Chen CC, Liou CM, Tsai WY. The effects of low-dose fentanyl on emergence agitation and quality of life in patients with moderate developmental disabilities. J Clin Anesth. [Journal Article; Randomized Controlled Trial]. 2005 2005-11-01; 17(7):494–8. PMID: 16297747

33. Finkel J, Cohen IT, Kim M, Hummer KA, Hannonah RS. Effect of Intranasal Fentanyl on Emergence Following Sevoflurane Anesthesia for BMT Surgery in Children. Anesthesiology Abstracts of Scientific Papers Annual Meeting. 2002(2000):.1252.

34. Galinkin JL, Fazi LM, Cuy RM, Kurth CD, Watcha MF. Intranasal Fentanyl in Children Undergoing Bilateral Myringotomy and Tube Placement. Anesthesiology Abstracts of Scientific Papers Annual Meeting. 2002(2000):.1253.

35. Cravero JP, Thyr B, Beach M, Whalen K. The Effect of Intravenous Fentanyl Agitation in Pediatric Patients. Anesthesiology Abstracts of Scientific Papers Annual Meeting. 2002(2001):.1222.

36. Zhang Y, Liu J, Wu X, Zhang W. Effect of dezocine on emergence agitation during recovery from sevoflurane-based anesthesia in children. Chinese Journal of Anesthesiology. 2012; 32(0254-1416(2012)32:12<1425:DZXDHE>2.0.TX;2-412):1425–8.
Binstock W, Rubin R, Bachman C, Kahana M, McDade W, Lynch JP. The effect of premedication with OTFC, with or without ondansetron, on postoperative agitation, and nausea and vomiting in pediatric ambulatory patients. Paediatr Anaesth. 2004;14(9):759. doi: 10.1111/j.1460-9592.2004.02375.x

OM A, M H, MY M, SS E. Comparative study between prophylactic single dose of fentanyl and dexmedetomidine in the management of agitation after sevoflurane anesthesia in children. Egyptian Journal of Anaesthesia. 2011(1):17.

Bakhamees HS, Mercan A, El-Halafawy YM. Combination effect of low dose fentanyl and propofol on emergence agitation in children following sevoflurane anesthesia. Saudi Med J. 2009;30(4):500–2. doi: 10.15537/smj.2009.4.30.500–2. PMID: 19370275

Demirbilek S, Togal T, Cicek M, Aslan U, Sizanli E, Ersoy MO. Effects of fentanyl on the incidence of emergence agitation in children receiving desflurane or sevoflurane anaesthesia. Eur J Anaesth. 2004;21(11):1128–35. doi: 10.1016/j.eja.2004.08.007. PMID: 15330959

Cravero JP, Beach M, Thyr B, Whalen K. The effect of small dose fentanyl on the emergence characteristics of pediatric patients after sevoflurane anesthesia without surgery. Anesth Analg. 2003;96(2):364–7. doi: 10.1213/01.ane.0000054728.48809.3b. PMID: 12873918

Galinkin JL, Fazi LM, Cuy RM, Chiavacci RM, Kurth CD, Shah UK, et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. Anesthesiology. 2004;100(3):542–7. doi: 10.1093/aneur/100.3.542. PMID: 15039838

Leao MM, Demirbilek S, Togal T, Cicek M, Aslan U, Sizanli E, Ersoy MO. Effects of fentanyl on the incidence of emergence agitation in children following sevoflurane anesthesia. Eur J Anaesth. 2004;21(11):1128–35. doi: 10.1016/j.eja.2004.08.007. PMID: 15330959

Inomata S, Maeda T, Shimizu T, Satsumae T, Tanaka M. Effects of fentanyl administration at different periods on emergence agitation. Anaesth Intensive Care. 2009;37(4):571–8. doi: 10.1111/j.1744-0998.2009.01326.x. PMID: 19681413

Kim HG, Ban JS, Lee JM, Lee JH, Lee SG, Min BW. The Effect of Alfentanil on the Emergence Agitation after Sevoflurane Anesthesia in Children Undergoing Inguinal Herniorrhaphy. Korean Journal of Anesthesiology. 2005;49(3):370–5.

Park SY, Kim JY, Gwak HJ, Kim JH, Kim US. The Effect of Ketamine and Fentanyl on the Incidence of Emergence Agitation after Sevoflurane Anesthesia in Children undergoing Tonsillectomy. Korean Journal of Anesthesiology. 2005;49(4):502–6.
56. MY M, MA G, E H E, AA R, BS E. Prevention of pediatric emergence agitation after sevoflurane anesthesia using preoperative rectal acetaminophen and intraoperative IV fentanyl. Egyptian Journal of Anaesthesia. 2009(4): .

57. Zhang C, Li J, Zhao D, Wang Y. Prophylactic midazolam and clonidine for emergence from agitation in children after emergence from sevoflurane anesthesia: a meta-analysis. Clin Ther. [Journal Article; Meta-Analysis; Research Support, Non-U.S. Gov't; Review]. 2013 2013-10-01; 35(10):1622–31. doi: 10.1016/j.clinthera.2013.08.016 PMID: 24075150

58. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg. [Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.]. 1998 1998-04-01; 86(4):781–5. PMID: 9539601

59. Costi D, Cyna AM, Ahmed S, Stephens K, Strickland P, Ellwood J, et al. Effects of sevoflurane versus other general anesthesia on emergence agitation in children. Cochrane Database Syst Rev. [Journal Article; Meta-Analysis; Research Support, Non-U.S. Gov't; Review]. 2014 2014-01-20; 9:D7084.

60. Finkel J, Cohen IT, Kim M, Hummer KA, Hannallah RS. Effect of Intranasal Fentanyl on Emergence Following Sevoflurane Anesthesia for BMT Surgery in Children. Anesthesiology Abstracts of Scientific Papers Annual Meeting. 2002(2000):1252.

61. Locatelli BG, Ingelmo PM, Emre S, Meroni V, Minardi C, Frawley G, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Paediatric Anaesthesia Emergence Delirium scale. Paediatr Anaesth. [Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2013 2013-04-01; 23(4):301–8. doi: 10.1111/pan.12038 PMID: 23043512

62. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg. [Clinical Trial; Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 1998 1998-11-01; 86(5):917–20. PMID: 8995263

63. Oh AY, Seo KS, Kim SD, Kim CS, Kim HS. Delayed emergence process does not result in a lower incidence of emergence agitation after sevoflurane anesthesia in children. Acta Anaesthesiol Scand. [Clinical Trial; Journal Article; Randomized Controlled Trial]. 2008 2008-03-01; 49(3):297–9. PMID: 15752391

64. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatr Anaesth. [Comparative Study; Journal Article]. 2010 2010-08-01; 20(8):704–11. doi: 10.1111/j.1460-9592.2010.03328.x PMID: 20497353

65. Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. Anesth Analg. [Journal Article]. 2007 2007-01-01; 104(1):84–91. PMID: 17179249

66. Juni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. [Journal Article; Research Support, Non-U.S. Gov't]. 2002 2002-02-01; 31(1):115–23. PMID: 11914306