

The effect of small dose sufentanil on emergence agitation in preschool children following sevoflurane anesthesia for elective repair of unilateral inguinal hernia

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ABSTRACT

الأهداف: إجراء دراسة مقارنة عن السوفنتانيل والفنتانيل في الحدوث المتكرر للتهيج عند الأطفال المرضى في هذه الدراسة.

الطريقة: تم ادخال 80 طفل دون سن المدرسة إلى قسم جراحة الأطفال في مستشفى ميانانغ المركزي خلال الفترة من مارس 2011م و أبريل 2012م، تم اختيار استخدام تخدير السيفوفلوران للاصلاح الاختياري للفتق الأربي من جانب واحد في هذه الدراسة الاسترجاعية، والعشوائية، والمزدوجة التعمية. أعطى الأطفال جرعة عبر الوريد من السوفنتانيل 0.15ug/kg أو الفنتانيل 1.5ug/kg قبل شق الجلد. تم قياس مستوى حدوث التهيج وعدد مرات تكرره بشكل حاد. تم تسجيل عدد المرضى الذين احتاجوا لجرعة إضافية من الفنتانيل خلال الجراحة و قياس الفنتانيل المستخدم بعد العملية الجراحية. وتم تقييم وقت النقاها والآثار سلبية أيضاً.

النتائج: كانت النتائج المتوسطة لحدوث التهيج منخفضة بشكل ملحوظ لدى مجموعة السوفنتانيل بالمقارنة بمجموعة الفنتانيل (9.1±3.5 versus 12±3.8 95%CI [1.27±0.53], $p=0.001$). كانت نسبة تكرار حدوث التهيج الحاد 27.5% لدى مجموعة السوفنتانيل، و5% لدى مجموعة الفنتانيل ($p=0.039$). أعطى عدد قليل من أطفال مجموعة السوفنتانيل جرعة إضافية من الفنتانيل أثناء الجراحة بالمقارنة بمجموعة الفنتانيل (5% versus 20%) ($p=0.043$) وعدد قليل أيضاً من أطفال مجموعة السوفنتانيل أعطوا جرعة واحدة من الفنتانيل بالمقارنة بمجموعة الفنتانيل (17.5% versus 42.5%; $p=0.015$). كانت نسبة حدوث التقيؤ لدى مجموعة الفنتانيل مرتفعة بشكل ملحوظ من مجموعة السوفنتانيل ($p=0.023$).

خاتمة: استخدام تخدير السيفوفلوران للأطفال دون سن المدرسة للاصلاح الاختياري للفتق الأربي من جانب واحد بالمقارنة بجرعة واحدة من الفنتانيل 1.5ug/kg والسوفنتانيل 0.15ug/kg قبل شق الجرح مما يقلل من حدوث التهيج بشكل ملحوظ بدون التسبب في تأخير وقت النقاها.

Objectives: To conduct a comparative study of sufentanil and fentanyl on emergence agitation in pediatric patients.

Methods: We conducted a prospective, randomized, and double-blind study in 80 preschool children admitted at the Pediatric Surgery, Mianyang Central

Hospital, Sichuan, China between March 2011 and April 2012. They underwent sevoflurane anesthesia for elective repair of unilateral inguinal hernia. Children received a single intravenous dose of sufentanil 0.15 ug/kg or fentanyl 1.5ug/kg just before skin incision. The emergence agitation scale and the frequency of severe emergence agitation were measured. Patients who required additional fentanyl during surgery and postoperative rescue fentanyl were recorded. Recovery time and the incidence of adverse effects were assessed.

Results: The mean emergence agitation scores were significantly lower in the sufentanil group compared with the fentanyl group (9.1±3.5 versus 12±3.8; 95% confidence interval [1.27±0.53]; $p=0.001$). The frequency of severe emergence agitation was 27.5% in the sufentanil group and 50% in the fentanyl group ($p=0.039$). Significantly fewer children in the sufentanil group received additional fentanyl during surgery compared to the fentanyl group (5% versus 20%; $p=0.043$) and significantly fewer children in the sufentanil group received one dose of postoperative rescue fentanyl compared to the fentanyl group (17.5% versus 42.5%; $p=0.015$). The incidence of vomiting was significantly higher in the fentanyl group than in the sufentanil group ($p=0.023$).

Conclusions: In preschool children undergoing repair of unilateral inguinal hernia with sevoflurane anesthesia, compared with a single dose of 1.5ug/kg fentanyl, 0.15ug/kg sufentanil before skin incision can significantly decrease the incidence of emergence agitation without delaying the recovery time.

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Due to relatively pleasant odor, hemodynamic stability, and rapid action and recovery,¹ sevoflurane is commonly used as an inhalational agent in pediatric patients, but postoperative emergence agitation (EA), also called emergence delirium, the excited and disoriented behavior on awakening from general anesthesia, is a frequent problem in children recovering from sevoflurane anesthesia.² Up to now, the exact etiology of EA is unknown, but it is more frequently observed in preschool children, and postoperative pain is regarded as a major contributing factor.^{3,4} Fentanyl was found to protect against EA,⁵⁻⁷ sufentanil is a very potent opioid receptor agonist, sufentanil is even more potent than fentanyl.⁸ We hypothesized that supplementing sevoflurane with sufentanil decreases the incidence and severity of EA while not delaying patient awakening and recovery after undergoing inguinal hernia repair. The purpose of the present study was to evaluate the effects of intraoperative intravenous administration a small dose of sufentanil on EA in preschool patients undergoing sevoflurane anesthesia for elective unilateral inguinal hernia repair, and compare it with fentanyl.

Methods. This is a prospective, randomized, and double-blind study conducted in 80 preschool children admitted at the Pediatric Surgery, Mianyang Central Hospital, Sichuan, China between March 2011 and April 2012. There were no changes to methods after trial commencement. Preschool children of age 2-6 years (classified as American Society of Anesthesiologists [ASA] physical status I or II)⁹ undergoing elective repair of unilateral inguinal hernia during sevoflurane general anesthesia were enrolled in the study. Patients were excluded if they were known allergic to any of the medications used, cardiovascular disease, kidney or liver dysfunction, neurologic disease, any sign of upper respiratory infection, a history of long-term therapeutic administration of analgesics, peptic ulceration, bleeding disorders, and body weight less than 10 kg or greater than 30 kg. Before skin incision, the patients received sufentanil 0.15 µg/kg (Group S) and fentanyl 1.5 µg/kg (Group F) intravenously, anesthesia was maintained with 3-5 vol% sevoflurane in oxygen without nitrous oxide (N₂O). Fentanyl 1 µg/kg was given to subjects in both groups for an increase in heart rate or systolic blood pressure 30% above preincision values that

continued for 5 minutes. The agitated children received an intravenous rescue fentanyl 1 µg/kg.

Main outcome measures. The pediatric anesthesia emergence delirium (PAED)¹⁰ scale, which consisting of 5 items: (1) the child makes eye contact with the caregiver, (2) the child shows purposeful actions, (3) the child is aware of his or her surroundings, (4) the child is restless, and (5) the child is inconsolable. Items 1-3 are scored as follows: 4=not at all, 3=just a little, 2=quite a bit, 1=very much, and 0=extremely. Items 4 and 5 are scored as: 0=not at all, 1=just a little, 2=quite a bit, 3=very much, and 4=extremely. The score for each item was summed up to get a total PAED scale score, and the highest scores were recorded. The frequency of severe emergence agitation (a 4-point scale):¹¹ agitation score was graded as 1 if the child was calm; 2 if the child was not calm, but could be easily consoled; 3 if the child was moderately agitated or restless and not easily calmed; and 4 if the child was combative, excited, or disoriented. Scores 1 and 2 were regarded as non-behavioral change, and scores 3 and 4 to indicate EA. Secondary outcome were number of patients who required additional fentanyl during surgery, postoperative rescue fentanyl at the postanesthesia care unit (PACU), and the incidence of adverse effects. There were no changes to trial outcomes after the trial commenced. Assuming an incidence of postoperative agitation of 50% or more supplementing sevoflurane with fentanyl was previously reported, and a 50% reduction in agitation was considered to be clinically significant, we calculated that 40 patients were required in each group. Two interim analyses were performed during the trial. The levels of significance maintained an overall *p*-value of 0.05.

Subjects were randomly allocated to one of 2 groups using a computer-generated random number assignment, sufentanil group (Group S: n=40) and fentanyl group (Group F: n=40). Randomization sequence was created using Stata 10.0 statistical software. The same PACU nurse who was unaware of the group to which the child was assigned collected the recordings of all variables. The study drugs were prepared by a trained nurse (who was not involved in any other part of the study) into identical 5ml syringes that were sequentially numbered. The children and anesthesiologists were unaware of the group to which the children were assigned. The intravenous agents were prepared and hidden behind drapes. The recordings of all variables were collected by the same PACU nurse who was unaware of the group to which the child was assigned. All children received an intravenous midazolam 0.1 mg/kg 5 minutes before entering into the operating room. Anesthesia was induced with 8 vol% sevoflurane in 100% oxygen via

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facemask without neuromuscular blocking agents. After achieving adequate depth of anesthesia, a laryngeal mask airway was inserted for airway maintenance, pressure-controlled ventilation was adapted to maintain end-tidal carbon dioxide (CO₂) levels between 35 mm Hg and 45 mm Hg. Intravenous ketorolac 0.5 mg/kg was administered to each child immediately after induction of anesthesia for the control of postoperative pain. All children receiving the same type surgery so as to get rid of the effects of these factors on EA.

Statistical analysis. Quantitative variables were described as mean and SD, qualitative variables were described as number and percentage, chi-square test was used to compare qualitative variables between groups, fisher exact test was used instead of Chi-square when one expected cell or more, ≤ 5 . Independent-samples t-test was used to compare the 2 groups as regards to quantitative variables. A *p*-value less than 0.05 was considered to be statistically significant in all tests.

Results. The study was conducted from March 2011 to April 2012 and all the children were observed until discharged from the PACU to general ward. Flowchart of 80 children (n=40 in the sufentanil group and n=40 in the fentanyl group) through the trial are shown in Figure 1.

There were no significant differences between the 2 groups with respect to age, weight, gender, ASA physical status, duration of surgery or duration of anesthesia (Table 1). The mean scores of the PAED scale and the incidence of emergence agitation were significantly

lower in the sufentanil group as compared with those in the fentanyl group ($p=0.001$ and $p=0.039$), there were no significant differences between the 2 groups in terms of emergence time and during stay in PACU (Table 2). The number of children who received additional fentanyl during surgery were significantly lower in sufentanil group compared to fentanyl group ($p=0.043$) and significantly fewer patients in the sufentanil group received 1 dose of postoperative rescue fentanyl at the PACU compared to the fentanyl group ($p=0.015$) as shown in Table 3. A comparison of postoperative adverse events between the 2 groups is presented in Table 4. The incidence of vomiting was significantly higher in the fentanyl group than in the sufentanil group ($p=0.023$). There were no differences between the 2 groups in terms of the incidence of laryngospasm, oxygen desaturation or pruritus.

Discussion. In recent years, sevoflurane has been widely used in children for general anesthesia induction and maintenance due to its low blood-gas solubility and blood-tissue solubility,¹² but EA is a common and difficult to deal with problems faced by the pediatric anesthesiologists,¹³ and it is potentially dangerous to the child, such as falling out of bed, the removal of the surgical dressings, intravenous catheters, and so on. Additional care may need when children are excited. Their parents are often worried when seeing their children restlessness.¹⁴ The young age, head and neck surgery, anesthesia drugs, preoperative anxiety, awakening in a hostile environment and postoperative

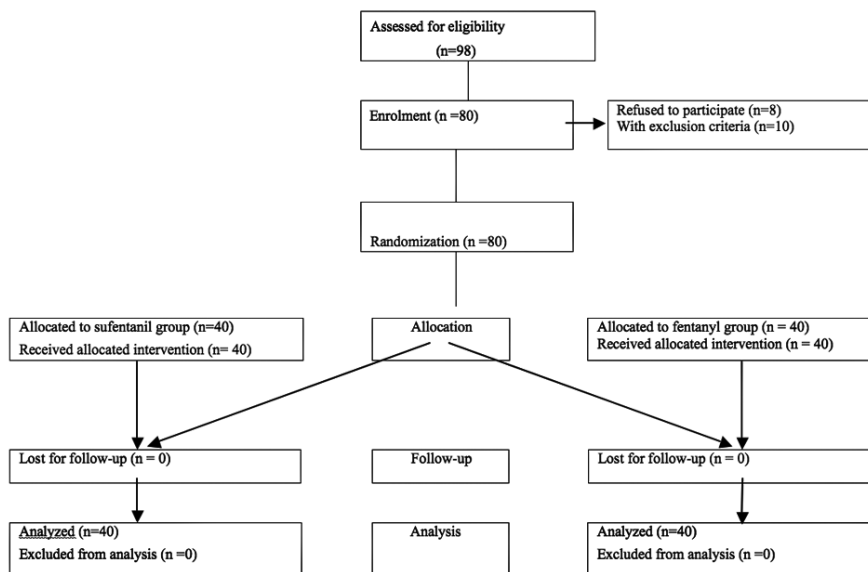


Figure 1 - Flowchart of 80 children (n=40 in the sufentanil group and n=40 in the fentanyl group) through the trial.

pain are risk factors for EA.¹⁵ Many studies have shown that EA in pediatric anesthesia is related to preoperative anxiety of the children.^{11,16} In this study, in order to relieve the emotional stress in children before surgery, premedication with an intravenous midazolam 0.1 mg/kg was given before separating from their parents, rather than oral midazolam in most studies, as the former is rapid onset of action. Type of surgery is also a predisposing factor of EA.¹⁷ In the present study, all children receiving the same type of surgery

was performed by the same surgeon enable to get rid of the effect of surgery on EA. Airway irritation reactions caused by tracheal intubation may lead to emergence behavior change, including EA.¹⁸ We used LMA for control ventilation and pulled it out while in a deeply anesthetized state to avoid the effect of airway irritation on EA. Postoperative pain is one of the most important factors leading to EA, there were many studies that had confirmed a decrease of EA with the use of fentanyl.^{5,7,19} The frequency of severe agitation of the present study

Table 1 - Demographic data, surgical and anesthetic times of 80 preschool children admitted to the Pediatric Surgery, Mianyang Central Hospital, Sichuan, China.

Demographic data	Group F Mean±SD	Group S Mean±SD	P-value	95% Confidence interval
Age (year)	3.5 ± 1.2	3.4 ± 1.3	0.82	-0.75 to 0.35
Weight (kg)	15.1 ± 8.9	16.2 ± 9.7	0.45	-1.5 to 2.52
Gender (male/female)	33/7	32/8	0.78	-0.142 to 0.25
ASA I/II	35/5	36/4	0.72	-0.354 to 0.723
Surgery duration (min)	45.6 ± 13.3	43.9 ± 16.5	0.3	-1.7 to 1.3
Anesthesia duration (min)	61.2 ± 15.8	63.4 ± 17.1	0.36	-1.29 to 2.2

Data are mean±SD or numbers of patients, there was no difference in variables between the 2 groups.

Table 2 - Emergence agitation scores and recovery time of fentanyl 1.5 ug/kg (Group F) and sufentanil 0.15 ug/kg (Group S).

Emergence agitation scores and recovery time	Group F Mean±SD	Group S Mean±SD	P-value	95% Confidence interval
PAED scale score	12 ± 3.8	9.1 ± 3.5	0.001	1.27 to 4.53
Incidence of agitation (%)	20 (50)	11 (27.5)	0.039	-0.436 to - 0.004
Emergence time(min)	15.05 ± 3.19	16.13 ± 3.65	0.165	-0.42 to 2.6
PACU time(min)	29.83 ± 6.43	27.9 ± 8.45	0.255	-1.42 to 5.27

The mean scores of the pediatric anesthesia emergence delirium (PAED) scale and the incidence of severe emergence agitation were significantly lower in the sufentanil group compared with the fentanyl group. PACU - post-anesthesia care unit

Table 3 - Number of children who received additional fentanyl during surgery.

Fentanyl administration	Group F n (%)	Group S n (%)	P-value	95% Confidence interval
Additional fentanyl during surgery	8 (20.0)	2 (5.0)	0.043	0.002 to 0.328
<i>Postoperative rescue fentanyl</i>				
1 dose	17 (42.5)	7 (17.5)	0.015	0.082 to 0.479
>1 dose	3 (7.5)	4 (10.0)	1.0	-0.144 to 0.093

Number of patients received additional fentanyl during surgery and 1 dose of postoperative rescue fentanyl in the post-anesthesia care unit were significantly lower in the sufentanil group compared to the fentanyl group.
Group F - fentanyl 1.5 ug/kg, Group S - sufentanil 0.15 ug/kg

Table 4 - Comparison of postoperative adverse events between the 2 groups.

Side effects	Group F n (%)	Group S n (%)	P-value	95% Confidence interval
Vomiting	9 (22.5)	2 (5.0)	0.023	0.061 to 0.318
Laryngospasm	1 (2.5)	0	1.0	0.000 to 0.091
Oxygen desaturation	3 (7.5)	1 (2.5)	0.608	-0.050 to 0.191
Pruritus	2 (5.0)	4 (10.0)	0.671	-0.186 to 0.064

The incidence of vomiting was significantly higher in the fentanyl group than in the sufentanil group.
Group F - fentanyl 1.5 ug/kg, Group S - sufentanil 0.15 ug/kg

is inconsistent with the results of another study investigating the prophylactic effects of fentanyl on EA;⁴ however, LMA was used for airway maintenance and removed it while in a deeply anesthetized state in this study, but tracheal intubation was performed in that study. Also, intravenous ketorolac was administered to child for the control of postoperative pain in the present study, but there was no analgesic for the control of postoperative pain. As fentanyl, sufentanil is also a pure μ agonist, but it is approximately 10 times as potent as fentanyl in human;²⁰ thus, we studied the effect of 0.15 ug/kg sufentanil on EA and compared it with 1.5 ug/kg fentanyl. Emergence agitation may also occur in the case of adequate treatment of pain or even no pain.²¹ In addition, according to a meta-analysis, there are no correlation of the efficacy of ketamine, α_2 -agonists, or fentanyl in postoperative pain relief and EA decreasing.⁵ These results suggest that the analgesic properties are not only involved in their prevention of EA, another properties may play a role against EA. As sufentanil is more lipophilic than fentanyl,²² it will allow the drug to penetrate the blood-brain barrier rapidly, resulting in sufficient sedation effect, and we speculate this is the cause of the incidence of agitation in the sufentanil group was significantly lower than that of fentanyl group. The protective effect of fentanyl on EA may be through the hypocretin system, because opioids can directly or indirectly inhibit the hypocretin system.²³ Opioids can lead to postoperative nausea and vomiting,²⁴ the incidence of vomiting was significantly higher in the fentanyl group than that in the sufentanil group, this is probably due to a reduction in children exposure to postoperative rescue fentanyl. As we worry about the additional sufentanil may result in delayed recovery, additional fentanyl was given to children during surgery or at the PACU, instead of giving sufentanil.

Study limitation. In the present study, we did not compare the pain score between the 2 groups as we focused on the effects of sufentanil on EA in preschool patients undergoing sevoflurane anesthesia. Another limitation of our study is the absence of a placebo-controlled group due to the rejection by our Hospital Ethics Committee.

In conclusion, this study demonstrated that the intravenous administration of a single dose of 0.15 ug/kg sufentanil just before skin incision decreases significantly the incidence of EA, reduces the adverse reactions by additional analgesic and does not lengthen discharge time from the PACU in children undergoing inguinal hernia repair under sevoflurane anesthesia compared with a single dose of 1.5 ug/kg fentanyl. Further studies are needed to find the optimal dose of sufentanil for

prevention of EA in pediatric sevoflurane anesthesia and the extent to which reducing postoperative agitation when additional sufentanil rather than fentanyl was given to children or sufentanil was given to children at the end of surgery, instead of skin incision.

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