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PAEDIATRICS

Effects of fentanyl infusion on tracheal intubation and emergence agitation in preschool children anaesthetized with sevoflurane

S. Inomata*, T. Maeda, T. Shimizu, T. Satsumae and M. Tanaka

Department of Anesthesiology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba City, Ibaraki 305-8575, Japan

* Corresponding author. E-mail: inomatas@md.tsukuba.ac.jp

Key points

- Sevoflurane is widely used in paediatric anaesthesia but can cause emergence agitation.
- Fentanyl may improve conditions at intubation and emergence.
- This was studied in 150 unpremedicated children.
- Fentanyl reduced early postoperative agitation in a dose-dependent manner.

Background. Sevoflurane can be used as a sole agent for intubation in children, but studies have suggested that it is associated with emergence agitation. Fentanyl infusions can be used both to facilitate intubation and decrease emergence agitation. We investigated the effects of fentanyl on conditions at intubation and on emergence from sevoflurane anaesthesia without confounding nitrous oxide or premedication.

Methods. IRB approval and informed consent were obtained. Subjects comprised 150 ASA physical status I or II (age, 2–6 yr). Anaesthesia was induced with sevoflurane in oxygen and maintained using a predetermined concentration of sevoflurane. Subjects were randomly allocated to receive one of three doses of fentanyl: vehicle only (control group), a bolus dose of 1 μg kg^{-1} followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1} (F1 group), or a bolus dose of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1} (F2 group). Sevoflurane minimum alveolar concentration for tracheal intubation (MAC_{TI}) and emergence agitation score were assessed.

Results. MAC_{TI} values were 2.49%, 1.61%, and 1.16% in control, F1, and F2 groups, respectively ($P<0.05$). Agitation scores were 11.5, 7.0, and 2.6 in control, F1, and F2 groups, respectively ($P<0.05$).

Conclusions. Fentanyl infusion consisting of a bolus dose of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1} facilitates tracheal intubation and smooth emergence in children anaesthetized using sevoflurane.
Clinical trial registration: this study was started in 2000 and was finished in 2008. We had no registration number. IRB approval was obtained.

Keywords: anaesthetics opioid, fentanyl; anaesthetics volatile, sevoflurane; paediatrics; potency, anaesthetic, MAC

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Paediatric anaesthesiologists often intubate the trachea using only sevoflurane without a neuromuscular blocking agent.[1 2] As sevoflurane shows potent hypnotic activity but low analgesic effect,[3] a combination of sevoflurane and fentanyl should reduce the minimum alveolar concentration for tracheal intubation (MAC_{TI}). Another major problem associated with sevoflurane is the potential for emergence agitation, particularly in preschool children. Previous studies have shown that a bolus of fentanyl (i.v. 1 or 2.5 μg kg^{-1}, nasal 2 μg kg^{-1}) can reduce the incidence of severe emergence agitation after sevoflurane anaesthesia.[4–6] However, the dose-related effects of fentanyl on MAC_{TI} and emergence agitation without nitrous oxide (which can produce nausea)[7] and premedication (which can decrease agitation)[8] have yet to be examined in preschool children. We used a randomized, single-blind study to assess the effects of two doses of continuous fentanyl infusion on sevoflurane concentrations required for tracheal intubation and on the emergence agitation score in children anaesthetized using sevoflurane alone.

Methods

Subject selection

We studied 150 children (age, 2–6 yr) of ASA physical status I or II who were undergoing elective minor surface surgery under general anaesthesia. The study protocols were

approved by the clinical investigation ethics committee of Tsukuba University (IRB), and informed consent was obtained from a parent or a guardian. Patients with airway malformation, clinical evidence of a difficult airway, asthma, or any sign of upper respiratory infection were excluded. Patients taking central nervous system (CNS) depressants or antiseizure medication, or who had CNS disorders including spinal cord dysfunction, developmental delay, or autism, were also excluded. The required numbers for each group in this study were calculated using power analysis to find a significant difference of $P<0.05$ ($\alpha=0.05$) with a power of 95% (β error=0.05). This analysis determined 45 patients per group as sufficient.

General procedure

Subjects were fasted for ≥4 h before induction of anaesthesia and did not receive premedication. A precordial stethoscope was used to monitor heart and breath sounds. Routine monitoring (AS/3™ monitoring system; Datex, Helsinki, Finland) was applied, including pulse oximetry, non-invasive arterial pressure, and electrocardiography. Body temperature was monitored by a tympanic probe and maintained at 36.8°C (0.4°C) using a heating pad. Inspired/end-tidal sevoflurane and carbon dioxide concentrations were measured with a multigas analyzer (AS/3) precalibrated automatically before each use. End-tidal concentrations were measured using the sampling tube attached to the L-connecter of the face mask before tracheal intubation and from the L-connecter at the proximal end of the tracheal tube (Portex™; Portex, Hythe, UK) after intubation. The end-tidal carbon dioxide trace had returned to zero and good (square) wave formation was present with a plateau and a total gas inflow of 6 litre min^{-1}. The end-tidal concentration of carbon dioxide was maintained at 4.7–5.3 kPa during the study.

Subjects were randomly allocated to one of three groups ($n=50$ per group) using computer-generated numbers to receive one of three doses of i.v. fentanyl: control group (saline); F1 group, a bolus of 1 μg kg^{-1} followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1}; or F2 group, a bolus of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1}. Continuous dose regimens were determined based on the results of a pilot study (data not shown). Subjects who received a trial dose (bolus dose of 2 μg kg^{-1} followed by a continuous infusion of 2 μg kg^{-1} h^{-1}) showed very smooth tracheal intubation, but drowsiness after emergence from anaesthesia, so we selected the doses mentioned above. End-tidal sevoflurane concentrations and intervals used in this study were determined based on the results of our pilot study (data not shown).

Experimental protocol

Measurement of sevoflurane concentration to prevent coughing on tracheal intubation (MAC_{TI})

Anaesthesia was induced with 5% sevoflurane in oxygen without i.v. anaesthetics and neuromuscular blocking agents. Spontaneous respiration was initially assisted, then controlled manually. After obtaining an i.v. cannula, the concentration of sevoflurane was decreased to the test concentration. After reaching a predetermined value, the end-tidal sevoflurane concentration was kept constant, and the ratio of predetermined end-tidal to inspiratory concentration was maintained at 0.95–1.00% for 5 min (stable status) before the initiation of fentanyl infusion.

When the simulated effect-site concentration of fentanyl increased to its maximum concentration (3 min after establishing stable offend-tidal sevoflurane concentration and starting fentanyl injection), laryngoscopy and tracheal intubation were quickly attempted using a curved blade and an uncuffed tracheal tube [size selected using the formula: internal diameter (mm)=4+age/4] without a neuromuscular blocking agent. Each sevoflurane concentration at which laryngoscopy and tracheal intubation were attempted was chosen by the anaesthesiologist in charge of each case (1.5–3.5% in the control group, 0.75–3.0% in the F1 group, and 0.75–2.5% in the F2 group). The step size of sevoflurane was 0.25%. The lowest concentration (1.5%) of sevoflurane in the control group was chosen based on the results of our previous study, which determined MAC_{TI} values of sevoflurane alone in children.[1] For the F1 and F2 groups, the lowest concentration of sevoflurane was reduced to half that of the control group (0.75%). The highest concentration of sevoflurane in each group was increased to inhibit positive responses in 100% of subjects. A single measurement was obtained per subject. Tracheal intubation accomplished without coughing, bucking, or gross purposeful muscular movements was considered smooth as determined by a nurse and a surgeon blinded to sevoflurane concentration and fentanyl dose. Subjects who moved during laryngoscopy or after tracheal intubation were immediately given 4–5% sevoflurane. Anaesthesiologists with 1–2 yr experience (>300 cases, including >50 paediatric cases) performed the tracheal intubation. Techniques required in intubations in children were enhanced using a paediatric patient simulator. The time for tracheal intubation was defined as the time from discontinuation of face-mask ventilation to connection of the tracheal tube to the anaesthesia circuit. Anaesthesia was then maintained with sevoflurane in oxygen at 1 litre min^{-1} and in air at 5 litre min^{-1}. The sevoflurane concentration was controlled according to the haemodynamics of each patient [maintaining systolic arterial pressure (SAP), heart rate (HR), or both changes within 20% of baseline].

Assessment of emergence agitation

Subjects received a field block using 2–3 ml of ropivacaine (0.3–0.5%) before the start of surgery. Rescue ropivacaine was infiltrated intraoperatively into s.c. tissue and into the surgical field, if necessary. The airway was gently suctioned, if necessary. Upon completion of surgery, sevoflurane was discontinued. Controlled ventilation at the same settings and a total gas flow of 6 litre min^{-1} of oxygen were continued without attempts to stimulate the patient. Spontaneous respiration was initially assisted and then adequate

spontaneous breathing was established. With the return of the cough reflex, patients were allowed to breathe spontaneously. When patients demonstrated complete emergence from anaesthesia by displaying a regular respiratory pattern, facial grimacing, and purposeful movement, the trachea was extubated and oxygen (6 litre min^{-1}) was administered via the mask. During emergence, subjects were observed for respiratory complications such as breath-holding and muscle rigidity, and for arterial oxygen desaturation. Subjects were kept in the operating theatre until achieving a post-anaesthetic recovery score of 9 or 10 [defined as a score of good (two points), fair (one point), or poor (zero point)] for each of five factors; consciousness, respiration, haemodynamic status, skin colour, and muscle force.[9] I.V. infusion of fentanyl was then discontinued, and patients were transferred to the general ward. The time to extubation from discontinuation of sevoflurane (extubation time) and the time to recovery (recovery score 9 or 10) from discontinuation of sevoflurane (recovery time) were recorded.

Although, several authors have reported two- to four-point rating scores to assess agitation,[8 10 11] we used the paediatric anaesthesia emergence delirium (PAED) scale,[12] a five-point rating scale with five gradations for each item that has been validated to assess emergence agitation in children. The PAED scale consists of five items: (1) the child makes eye contact with the caregiver, (2) the child shows purposeful actions, (3) the child is aware of their surroundings, (4) the child is restless, and (5) the child is inconsolable. Items (1)–(3) are reversed 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 follows: 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 to obtain a total PAED scale score. Overall emergence agitation after tracheal extubation was continually assessed by an anaesthesiologist blinded to the treatment group for 15 min until transfer to the general ward. The score that lasted the longest was regarded as the agitation score. We considered patients who complained of pain, tried to remove the surgical dressing after surgery to have pain, or both, and provided additional bolus injections of fentanyl at 1 μg kg^{-1}. These patients were excluded from the study.

Data analysis

Subject characteristics and clinical details are provided as mean values [standard deviation (SD)]. Statistical comparisons among the three groups (control, F1, and F2) were performed using analysis of variance (ANOVA) with the Scheffe test for *post hoc* analysis (StatView software; SAS Institute, Cary, NC, USA). Statistical comparisons within each group were performed using repeated-measures ANOVA, and significance was assessed using the Scheffe test. Sex, ASA physical status, and surgical procedure were analysed using Fisher's exact test. In all cases, values of $P<0.05$ were considered the minimum level for statistical significance. We determined the preventive sevoflurane concentration against coughing on tracheal intubation using a multiple independent variable logistic regression model (SAS System version 6.12; SAS Institute).

Results

Subject characteristics and clinical details other than haemodynamic changes were very similar between groups with (Table 1) no differences in baseline SBP or HR. Both SBP and HR before intubation decreased below baseline values in all three groups. Thereafter, both SBP and HR increased after intubation to baseline values in all three groups. SBP in the F2 group did not significantly increase compared with the value before intubation. In the F2 group, both SBP and HR immediately after intubation were lower than those values in the control group. Thereafter, both SBP and HR values were similar in the three groups. Time for tracheal intubation did not exceed 15 s. No patients showed breath-holding, muscle rigidity, vomiting, arterial oxygen desaturation, bradycardia, or hypotension necessitating treatment.

A total of four control-group subjects, five F1-group subjects, and two F2-group subjects were excluded from the study after administration of additional bolus injections of fentanyl at 1 μg kg^{-1} as rescue doses (Fig. 1).

Sevoflurane concentration for prevention of coughing on tracheal intubation (MAC_{TI})

Table 2 shows the end-tidal sevoflurane concentrations and percentages of patients with smooth tracheal intubation. Maximum likelihood estimators of logistic regression model parameters (χ^2 goodness of fit and *P*-value) were 0.978 and 0.0018 in the control group, 0.690 and 0.0086 in the F1 group, and 0.829 and 0.0040 in the F2 group, respectively (Fig. 2). Significant differences were identified between the three curves ($P<0.01$), and dose-related effects of fentanyl on sevoflurane MAC_{TI} were observed. The calculated MAC_{TI} values were 2.49% [confidence interval (CI), 2.22–2.81%], 1.61% (CI, 0.89–2.04%), and 1.16% (CI, 0.46–1.39%) for the control, F1, and F2 groups, respectively. The 95% effective dose values were 3.45% (CI, 3.02–5.15%), 3.22% (CI, 2.52–7.65%), and 1.97% (CI, 1.69–3.21%) for the control, F1, and F2 groups, respectively. Smooth tracheal intubation was possible in all groups at an end-tidal sevoflurane concentration of 3.25% in the control group, 2.75% in the F1 group, and 2.25% in the F2 group.

Assessment of emergence agitation

Emergence excitement after tracheal extubation was assessed continuously for all cases for 15 min until transfer to the general ward. The PAED scale scores were 11.5 (4.3), 7.0 (4.8), and 2.6 (1.7) in the control, F1, and F2 groups, respectively ($P<0.05$). The time to achieve extubation from discontinuation of inhaled anaesthetics did not exceed 15 min in any subject. Extubation times (from discontinuation of sevoflurane) were 7 (3), 7 (3), and 8 (3) min in the control, F1, and F2 groups, respectively ($P<0.05$). Recovery times (from discontinuation of sevoflurane) were 7 (3), 9

Table 1 Subject characteristics and clinical details. Values were presented as the mean (SD) or mean (range). *$P<0.05$ compared with control group. †$P<0.05$ compared with baseline. #$P<0.05$ compared with value before intubation. Control group, saline infusion; F1 group, a bolus dose of 1 μg kg^{-1} followed by a continuous dose of 0.5 μg kg^{-1} h^{-1}; F2 group, a bolus dose of 2 μg kg^{-1} followed by a continuous dose of 1 μg kg^{-1} h^{-1}

	Control group ($n=46$)	F1 group ($n=45$)	F2 group ($n=48$)
Age (yr)	3.8 (2–6)	3.6 (2–6)	3.8 (2–6)
Body weight (kg)	14 (7)	16 (8)	15 (7)
Sex (male/female)	20/26	23/22	25/23
ASA physical status I	42	43	42
ASA physical status II	4	2	6
Procedure			
Inguinal herniorraphy	19	30	26
Plastic surgery (nervous, ear, finger)	23	13	16
CV catheter insertion	4	2	6
Durations of			
Anaesthesia (min)	104 (49)	102 (41)	103 (52)
Surgery (min)	67 (46)	64 (40)	67 (47)
Range of ET sevoflurane during surgery (%)	1.5–2.5	1.5–2.5	1.5–2.5
Systolic arterial pressure (mm Hg)			
Baseline before induction	117 (12)	116 (12)	118 (13)
Before intubation	105 (14)†	106 (10)†	105 (15)†
After intubation	119 (14)#	117 (11)#	112 (12)*
Heart rate (beats min^{-1})			
Baseline before induction	117 (16)	116 (24)	119 (18)
Before intubation	99 (23)†	98 (23)†	98 (24)†
After intubation	123 (15)#	114 (25)#	110 (21)*#

(4), and 9 (4) min in the control, F1, and F2 groups, respectively ($P<0.05$).

Discussion

Sevoflurane has been used as a sole agent for intubation in children, but is associated with emergence agitation. Fentanyl was expected to both facilitate intubation and decrease emergence agitation. Since previous reports used nitrous oxide or premedication, the pure effects of sevoflurane on intubation and emergence were unknown in children. Fentanyl infusion as a bolus of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1} provided improved conditions for both intubation and emergence.

The MAC_{TI} for sevoflurane determined in the present study (2.49%) is slightly less than our previously reported value (2.69%).[1] This difference might be attributable to the step size in the MAC_{TI} determination (0.25% in the present study, to obtain more detailed data, compared with 0.5% in our previous study).[1] Logistic regression curves obtained in the current and previous studies (with a stabilization period of 15 min as the conventional method)[1] are similar (Fig. 3). Accordingly, the difference between end-tidal and cerebral concentrations of sevoflurane would be minimal, even though measured end-tidal sevoflurane concentrations do not correctly reflect concentrations in the brain. The MAC_{TI} value of 3.55 vol% in adults[13] is higher than that observed in children. This difference might be explained by the tracheal tube, which is cuffed in adults, but not in this study of children.

The frequency of severe agitation observed in a previous study[6] (a single bolus dose of fentanyl at 2.5 μg kg^{-1}) was 36%, whereas frequencies in this study (total PAED score >10)[12 14] were 33% in the F1 group and 2% in the F2 group. Two other studies have reported that a single bolus dose of fentanyl (1 μg kg^{-1} in one study,[4] and 2 μg kg^{-1} in the other)[5] reduces the incidence of severe emergence agitation after sevoflurane anaesthesia. However, in those studies and in a previous study[6] using fentanyl 2.5 μg kg^{-1}, subjects received adjuvant drugs (nitrous oxide[4–6] or midazolam)[4 5] in addition to sevoflurane. Numerous drugs, including benzodiazepines, barbiturates, and opioids, contribute to behavioural disturbances after general anaesthesia.[15] The use of premedication, such as oral midazolam 0.5 mg kg^{-1} and i.v. clonidine 2 μg kg^{-1}, decreases the amount of emergence agitation,[8 16] and nitrous oxide produces nausea.[7] Administration of these adjuvant drugs impedes assessment of side-effects or incidence of agitation emergence caused solely by sevoflurane (control group). Although the use of fentanyl was likely to decrease HR and SBP and produce nausea, no subjects required treatment for these effects in this study. The difference in incidences of agitation and vomiting between this study and a previous study[6] might partially depend on the period of observation

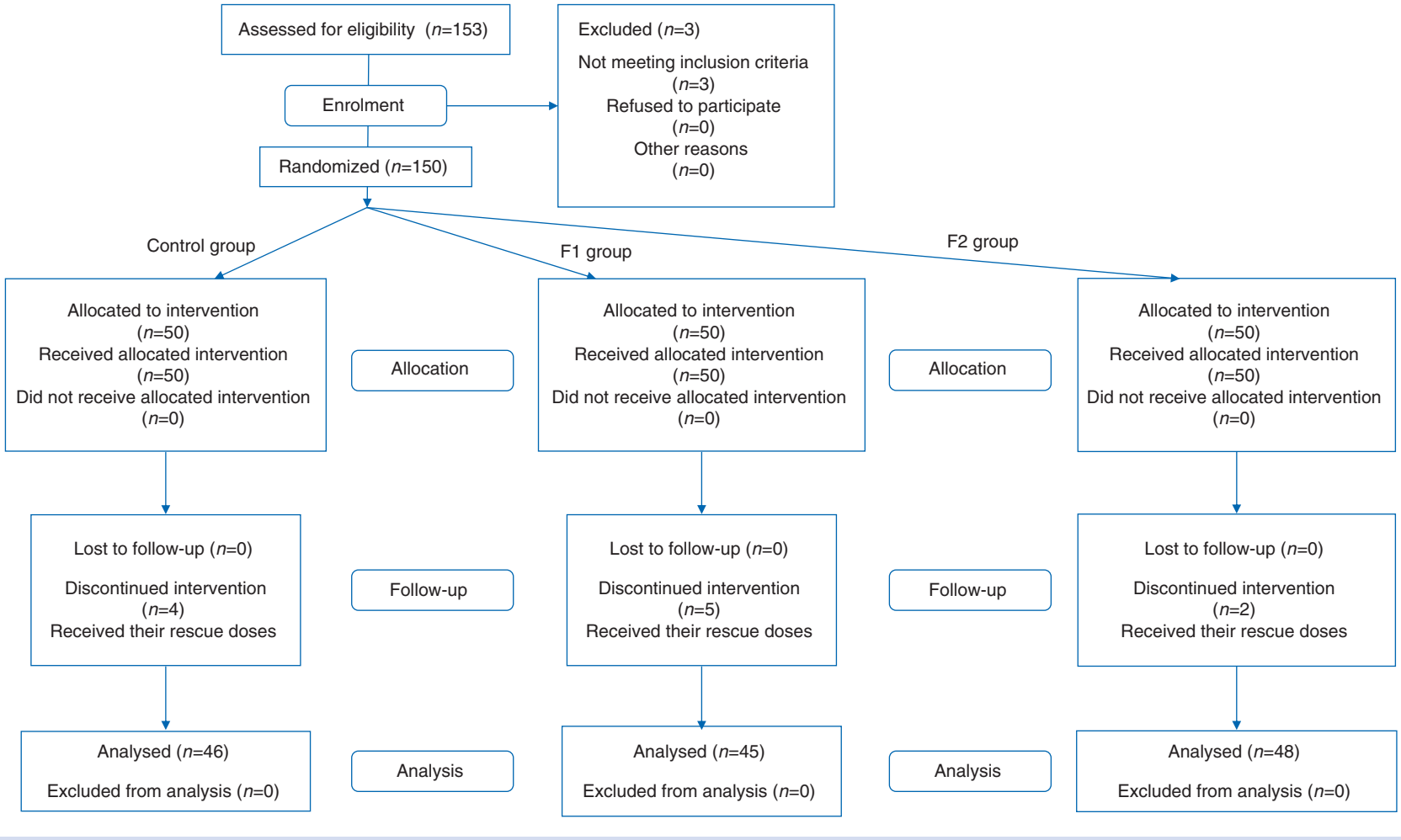

Fig 1 CONSORT diagram.

Table 2 Incidence of smooth tracheal intubation. Control group, saline infusion; F1 group, a bolus of 1 μg kg^{-1} followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1}; F2 group, a bolus of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1}

End-tidal sevoflurane concentration in each subgroup (vol%)	Control group (*n*=46)	F1 group (*n*=45)	F2 group (*n*=48)
0.75		0% (0/2)	0% (0/2)
1.00		33% (1/3)	33% (1/3)
1.25		33% (1/3)	67% (4/6)
1.50	0% (0/2)	55% (6/11)	82% (9/11)
1.75	0% (0/3)	50% (4/8)	88% (7/8)
2.00	33% (2/6)	60% (3/5)	92% (11/12)
2.25	30% (3/10)	67% (2/3)	100% (3/3)
2.50	50% (5/10)	75% (3/4)	100% (3/3)
2.75	60% (3/5)	100% (3/3)	
3.00	80% (4/5)	100% (3/3)	
3.25	100% (3/3)		
3.50	100% (2/2)		

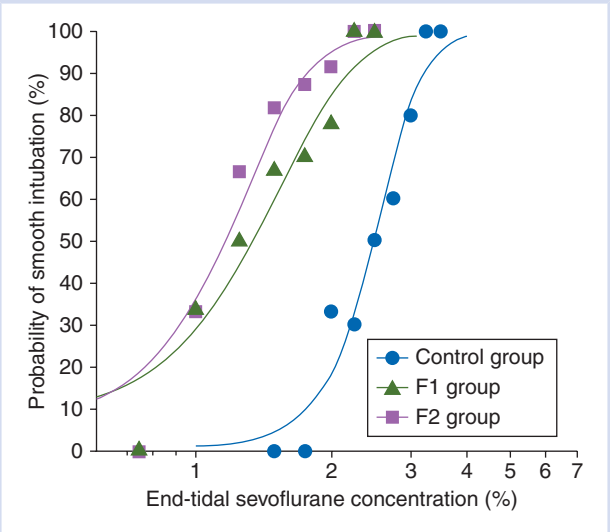

Fig 2 Dose–response curves for sevoflurane plotted from logistic analysis of individual end-tidal concentrations and the response to tracheal intubation. Subjects in the control group received saline. Subjects in the F1 group received a bolus of 1 μg kg^{-1} followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1}. Subjects in the F2 group received a bolus of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1}.

(15 min in this study and 24 h in the previous study). This is the first study to examine dose-related effects of continuously infused fentanyl on emergence agitation in preschool children without using nitrous oxide or premedication.

Several studies have reported emergence agitation in patients anaesthetized with sevoflurane even when pain was treated effectively or even when no pain was

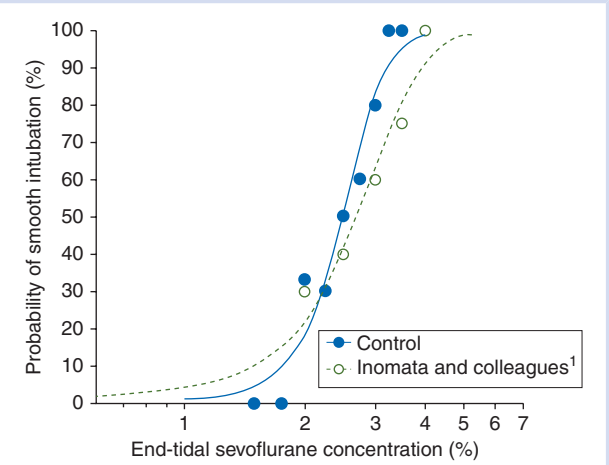

Fig 3 Dose–response curves for sevoflurane plotted from logistic analysis of individual end-tidal concentrations and the response to tracheal intubation in the current study (solid line and solid circles) compared with a previous study[1] (dashed line and open circles). Logistic regression curves obtained in the current and previous control groups are similar (P=0.5066). The concentrations for smooth intubation in 50% of subjects for the current and previous control groups were 2.49% and 2.69%, respectively.

present.[17 18] The present study was thus unable to elucidate why fentanyl efficiently reduced the incidence of agitation in children with pain treated using a field block. It is difficult for children, particularly given their preschool age, to articulate discomfort. Other than surgical pain, airway irritation caused by tracheal intubation could lead to behavioural manifestations, including emergence agitation. Emergence time in this study was similar among the three groups. Rapid awakening in an unfamiliar room thus might not be the main cause of emergence agitation.

A relationship between opioid and sedative status has recently been reported.[19] The hypothalamic hypocretin/orexin system regulates arousal and maintenance of the waking state. Hypocretin neurones are depressed by opioids which inhibit the hypocretin system by directly acting on the cell body and by indirectly reducing the excitatory synaptic tone through a presynaptic mechanism. These findings suggest that the low frequency of emergence agitation in patients receiving fentanyl might be influenced by the hypocretin system. In addition, a recent meta-analysis reported that the analgesic properties of opioids do not seem to play a role in prophylactic effects against emergence agitation.[20]

Some limitations need to be considered for the present study. In a pilot study using a bolus of 2 μg kg^{-1} fentanyl followed by a continuous infusion of 2 μg kg^{-1} h^{-1}, we observed smooth tracheal intubation, but subjects were drowsy and unresponsive on emergence. We therefore adopted a bolus dose of 2 μg kg^{-1} followed by a continuous infusion of 1 μg kg^{-1} h^{-1} in this study. A future study might assess other doses of fentanyl or overuse of sufentanil.[21] Secondly, this study enrolled patients undergoing several

types of surgeries; further study should be performed in subjects receiving the same surgery. Thirdly, Cravero and colleagues[4] reported a high incidence of agitation using a different method without a validated agitation scale. The agitation score can be determined as the highest score in an instant or the score that lasted the longest. When we adopted a longer observational period, a different criterion, or both, the results differ to some degree. Most previous studies have used the highest score in the observation period.[4–8 10–12] We regard the agitation period as important and therefore selected the score that lasted the longest as the agitation score. Future studies on agitation should consider both the score and the period (e.g. area under the curve).

In conclusion, we assessed the effects of continuous infusion of fentanyl on sevoflurane concentrations required for tracheal intubation and on conditions at emergence after surgery in preschool children. Fentanyl showed dose-related effects to smooth intubation and calm emergence in children anaesthetized with sevoflurane.

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Conflict of interest

Support was solely from departmental resources.

References

1 Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. *Anesthesiology* 1994; **80**: 93–6

2 Inomata S, Kihara S, Yaguchi Y, Baba Y, Kohda Y, Toyooka H. Reduction in standard MAC and MAC for intubation after clonidine premedication in children. *Br J Anaesth* 2000; **85**: 700–4

3 Tomi K, Mashimo T, Tashiro C *et al.* Alternations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; **70**: 684–6

4 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; **97**: 364–7

5 Galinkin JL, Fazi LM, Cuy RM *et al.* Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology* 2000; **93**: 1378–83

6 Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. *Anesth Analg* 2002; **94**: 1178–81

7 Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. *Br J Anaesth* 1999; **83**: 104–17

8 Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. *Paediatr Anaesth* 1999; **9**: 299–304

9 Aldrete JA. The postanesthesia recovery score revisited. *J Clin Anesth* 1995; **7**: 89–91

10 Davis PJ, Greenberg JA, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg* 1999; **88**: 34–8

11 Aono J, Ueda W, Mamiya K, Takimoto E, Manabe M. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. *Anesthesiology* 1997; **87**: 1298–300

12 Sikich N, Lerman J. Development and psychometric evaluation of the paediatric emergence delirium scale. *Anesthesiology* 2004; **100**: 1138–45

13 Katoh T, Nakajima Y, Moriwaki G *et al.* Sevoflurane requirements for tracheal intubation with and without fentanyl. *Br J Anaesth* 1999; **82**: 561–5

14 Aouad MT, Yazbeck-Karam VG, Nasr VG, EI-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* 2007; **107**: 733–8

15 Galford RE. *Problems in Anesthesiology: Approach to Diagnosis.* Boston, MA: Little, Brown & Company, 1992; 341–3

16 Fazi L, Jantzen EC, Rose JB, Kurth CD, Watcha MF. A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient. *Anesth Analg* 2001; **92**: 56–61

17 Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. *Paediatr Anaesth* 2000; **10**: 419–24

18 Uezono S, Goto T, Terui K *et al.* Emergence agitation after sevoflurane versus propofol in pediatric patients. *Anesth Analg* 2000; **91**: 563–6

19 Li Y, van den Pol AN. Mu-opioid receptor-mediated depression of the hypothalamic hypocretin/orexin arousal system. *J Neurosci* 2008; **28**: 2814–9

20 Dahmani S, Stany I, Brasher C *et al.* Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. *Br J Anaesth* 2010; **104**: 216–23

21 Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–41