

Use of Intranasal Fentanyl in Children Undergoing Myringotomy and Tube Placement during Halothane and Sevoflurane Anesthesia

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Background: Many children are restless, disoriented, and inconsolable immediately after bilateral myringotomy and tympanosotomy tube placement (BMT). Rapid emergence from sevoflurane anesthesia and postoperative pain may increase emergence agitation. The authors first determined serum fentanyl concentrations in a two-phase study of intranasal fentanyl. The second phase was a prospective, placebo-controlled, double-blind study to determine the efficacy of intranasal fentanyl in reducing emergence agitation after sevoflurane or halothane anesthesia.

Methods: In phase 1, 26 children with American Society of Anesthesiologists (ASA) physical status I or II who were scheduled for BMT received intranasal fentanyl, 2 $\mu\text{g}/\text{kg}$, during a standardized anesthetic. Serum fentanyl concentrations in blood samples drawn at emergence and at postanesthesia care unit (PACU) discharge were determined by radioimmunoassay. In phase 2, 265 children with ASA physical status I or II were randomized to receive sevoflurane or halothane anesthesia along with either intranasal fentanyl (2 $\mu\text{g}/\text{kg}$) or saline. Postoperative agitation, Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scores, and satisfaction of PACU nurses and parents with the anesthetic technique were evaluated.

Results: In phase 1, the mean fentanyl concentrations at 10 ± 4 min (mean \pm SD) and 34 ± 9 min after administering intranasal fentanyl were 0.80 ± 0.28 and 0.64 ± 0.25 ng/ml, respectively. In phase 2, the incidence of severe agitation, highest CHEOPS scores, and heart rate in the PACU were decreased with intranasal fentanyl. There were no differences between sevoflurane and halothane in these measures and in times to hospital discharge. The incidence of postoperative vomiting, hypoxemia, and slow respiratory rates were not increased with fentanyl.

Conclusions: Serum fentanyl concentrations after intranasal administration exceed the minimum effective steady state concentration for analgesia in adults. The use of intranasal fentanyl during halothane or sevoflurane anesthesia for BMT is associated with diminished postoperative agitation without an increase in vomiting, hypoxemia, or discharge times. (Key words: Agitation; analgesia; anesthetics; delirium; pediatric anesthesia; pharmacokinetics; postoperative complications.)

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BILATERAL myringotomy and tympanosotomy tube placement (BMT) is performed in approximately one million children annually in the United States, making it the most common pediatric surgical operation.¹ This ultrashort procedure is typically performed with the patient spontaneously breathing potent inhalation anesthetics and often without intravenous access. However, 25-50% of children undergoing BMT emerge from anesthesia restless, disoriented, and inconsolable.²⁻⁵ Sevoflurane, an inhalation agent with low solubility, is associated with a rapid induction and recovery with minimal airway irritation and cardiac depression, making it popular for BMT procedures. The benefits of faster emergence with sevoflurane compared with halothane anesthesia may be offset by increased emergence agitation.^{3,6-8} Postoperative pain has also been implicated as one of the many contributing factors for postoperative agitation.^{6,9-13} However, it is especially difficult to differentiate between pain-related behavior and emergence agitation in the young, preschool child.^{14,15}

Although this postoperative agitation is self-limiting, in our experience it is a major source of dissatisfaction for parents, nurses, and others taking care of these children. The absence of intravenous access makes it particularly difficult to achieve rapid control of these symptoms. Some investigators have recommended the routine prophylactic use of acetaminophen and nonsteroidal anti-inflammatory drugs such as ketorolac and ibuprofen before emergence from anesthesia.^{4,5,12,16,17} However, 30-55% of children receiving these medications required additional analgesia.^{3,12,17} These findings suggest that more potent analgesics may be required.^{2,5}

In the past, intravenous fentanyl 1-2 $\mu\text{g}/\text{kg}$ has been used to treat postoperative agitation in children.^{6,13} The intranasal route of opioid administration is an effective and rapid method of achieving analgesia in adults and children when intravenous access is not available.¹⁸⁻²³ However, there are no data available on the serum concentrations of fentanyl achieved with this route in children, and no data on the efficacy of intranasal fentanyl in reducing the incidence of postoperative agitation after halothane or sevoflurane anesthesia for BMT.

This two-phase study was designed to determine the efficacy of intranasal fentanyl in decreasing the incidence of adverse postanesthetic agitation after BMT in children. The first phase was an open-label study to determine serum concentrations after a single intraoperative nasal fentanyl dose (2 $\mu\text{g}/\text{kg}$). The second phase

was a double-blind placebo-controlled trial to determine the effect of intranasal fentanyl on the incidence of agitation after sevoflurane and halothane anesthesia in children undergoing BMT.

Materials and Methods

A total of 291 children (26 in phase 1 and 265 in phase 2) were studied after obtaining approval from the Children's Hospital Institutional Review Board (Children's Hospital of Philadelphia, Philadelphia, PA) and written informed consent from the parents or legal guardians. We limited enrollment in both phases to healthy children with American Society of Anesthesiologists (ASA) physical status I or II, age 9 months to 6 yr, and weight \leq 25 kg, who were scheduled for BMT procedures. All patients were fasted for 8 h for solids and 2 h for clear liquids. Patients with an allergy to fentanyl or midazolam or a history suggestive of an increased risk for developing malignant hyperthermia were excluded. We also excluded children who were at risk of airway obstruction (obstructive sleep apnea and craniofacial syndromes) or who had neurodevelopmental delay, cardiopulmonary disease, or an active history of untreated gastroesophageal reflux. All patients received acetaminophen 10 mg/kg and midazolam 0.5 mg/kg orally as preanesthetic medication approximately 30 min before induction of anesthesia.

Phase 1

After applying ASA-approved standard noninvasive monitoring, anesthesia was induced and maintained with sevoflurane and nitrous oxide *via* a facemask with spontaneous ventilation and additional ventilatory support if necessary. Fentanyl (50 μ g/ml) 2 μ g/kg was administered intranasally (1 μ g/kg in each nostril in four equal [0.5 μ g/ml] aliquots from a 1-ml syringe over 2–5 s) before the start of surgery, and the time was recorded. Patients with nasal congestion had their nostrils suctioned before intranasal fentanyl administration. All subjects then had an intravenous cannula inserted. A 2-ml aliquot of blood was drawn at the completion of surgery (time 1) and just before discharge from phase 1 postanesthesia care unit (PACU), approximately 30 min after arrival (time 2). Samples were immediately centrifuged, separated, and frozen at -70°C as per protocol for analysis. Fentanyl concentrations were determined by radioimmunoassay (Janssen Pharmaceutica, Beerse, Belgium).²⁴ This method has a minimum detectable concentration of 0.08 ng/ml with an intraassay and interassay coefficient of variability ranging from 4.6% to 5.9% and 5.0% to 7.1%, respectively.²⁴

Phase 2

We proceeded to phase 2 of the study after the results of phase 1 showed serum concentrations were achieved

in all subjects with intranasal fentanyl administration. In phase 2, 265 subjects were enrolled and randomly assigned to one of four study groups, according to a computer-generated random number table. Anesthesia was induced and maintained with sevoflurane–nitrous oxide in oxygen in groups 1 and 2, and with halothane–nitrous oxide in oxygen in groups 3 and 4. Fentanyl, 2 μ g/kg, was administered intranasally to groups 1 and 3, whereas groups 2 and 4 received saline placebo intranasally. Patients were permitted to breathe spontaneously, and ventilation was assisted when required. Preanesthetic medications and perioperative monitoring for phase 2 were the same as for phase 1.

In this phase it was not possible to blind the person administering the anesthetic regarding the use of sevoflurane or halothane, but they were informed of the group assignment only after enrollment of the child. The research observer, patient, parent, and nurses in the PACU were blinded to the inhalation agent used. The anesthesiologist, research observer, patient, parents, and PACU nurse were all blinded to the intranasal solution administered, which was drawn up by a third party who had no further involvement in the study.

After induction of anesthesia but before the start of surgery, the assigned intranasal solution was administered as in the first phase of the study, and the time was recorded. Nasal congestion was cleared by suction before administration of intranasal study drug. Adverse events such as hypoxemia, chest wall rigidity, laryngospasm, coughing, or bronchospasm were noted. The surgeon assessed the severity of the ear disease using previously described rating scale.³

The research observer recorded the subject's postoperative behavior and assessed the child's pain at 0, 5, 15, 30, 45, 60, 75, 90, 105, 120 min after arrival in the PACU. Postoperative behavior was assessed using a 1–4 scale (1 = calm; 2 = not calm but could easily be consoled; 3 = not easily calmed, moderately agitated, or restless; and 4 = combative, excited, or disoriented, thrashing around).^{2,6} Pain assessments were made using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), a validated multifactorial pain scale based on scores for cry, facial expression, verbal expression, and movement in infants and children.²⁵ In addition, the observer recorded heart rate, blood pressure, oxygen saturation, the need for supplemental oxygen, episodes of vomiting, adverse respiratory events (hypoxemia, respiratory rate \leq 16, laryngospasm, bronchospasm), and the time to achieve standard discharge criteria from both recovery phases. The nurses in phases 1 and 2 of the PACU assessed their satisfaction with patient behavior, using a 100-mm visual analog scale (0 = not satisfied, 100 = completely satisfied). Parents were contacted *via* telephone 24 h after surgery to determine the child's analgesic requirement, the incidence of nausea and vomiting, and time taken to return to the preoperative

Table 1. Demographic Data, Severity of Ear Discharge, Duration of Surgery, Anesthesia, and Hospital Stay in the Four Study Groups

	Sevoflurane + Nasal Fentanyl	Sevoflurane + Nasal Placebo	Halothane + Nasal Fentanyl	Halothane + Nasal Placebo
N	64	69	66	61
Age (months)	24 ± 15	24 ± 15	27 ± 16	24 ± 15
Weight (kg)	12.5 ± 3.3	12.5 ± 2.9	13.2 ± 3.2	12.5 ± 3.1
Gender (M/F)	42/22	49/20	36/30	39/22
Severity of ear disease				
Median score (interquartile range)	3 (1-4)	3 (1-4)	3 (1-4)	2 (1-3)
Duration of surgery (min)	5.1 ± 1.7	5.0 ± 1.7	4.8 ± 1.9	5.0 ± 1.7
Duration of anesthesia (min)	10.1 ± 3.2	10.2 ± 2.9	10.7 ± 3.9	10.4 ± 6.6
Time (min) from end of surgery until:				
Ready for discharge from hospital	68 ± 26	66 ± 23	73 ± 22	70 ± 20
Actual discharge from hospital	83 ± 27	82 ± 23	91 ± 36	84 ± 28

baseline state. Parents were also asked to rate their satisfaction with the anesthetic care on a 0-10-point verbal rating scale (0 = not satisfied, 10 = completely satisfied).

Statistical Analysis

Phase 1. Mean serum fentanyl concentrations were calculated. The incidence of nondetectable concentrations (< 0.08 ng/ml) was also noted.

Phase 2. The primary end point of the study was the incidence of severe postoperative agitation, which was defined as a behavior rating scale of 4. Sample size calculations were based on a comparison of proportions in independent samples. We assumed the incidence of adverse behavior in the placebo group would be 25%^{5,12,16} and considered a reduction in this incidence to 5% to be of clinical importance. A sample size of 60 in each group would give an 80% chance of detecting this difference at the 0.05 level of significance ($\alpha = 0.05$, $\beta = 0.2$). We recruited 66 patients per group or a total of 264 patients to allow for a possible 10% drop-out rate.

Continuous variables with a normal distribution were compared among groups using one-way analysis of variance tests. If a significant difference was noted, intergroup comparisons were made using the Student-Neuman-Keuls test. If these variables did not have a normal distribution, nonparametric Kruskal-Wallis analysis of variance was used. Categorical variables were compared using a chi-square test with continuity correction or a Fisher exact test where applicable. Data are presented as mean ± SD values for normally distributed data, median with interquartile range for skewed data, and number or percentage. A *P* value less than 0.05 was considered statistically significant.

Results

Phase 1

We obtained blood samples from all 26 patients at time 1 (10 ± 4 min after administering intranasal fentanyl) and 25 of 26 patients at time 2 (34 ± 9 min after

intranasal administration). All children had detectable levels of fentanyl at both time points. Serum concentrations at time 1 were 0.80 ± 0.28 ng/ml (range, 0.24-1.43 ng/ml) and at time 2 were 0.64 ± 0.25 ng/ml (range, 0.30-1.12 ng/ml). There were no adverse respiratory events related to study drug administration.

Phase 2

Two hundred sixty-five patients were enrolled, but 10 protocol violations occurred in five cases. In four of them there was an inadvertent use of both inhalation agents (halothane and sevoflurane). One patient developed laryngospasm on induction of anesthesia before the intranasal solution was administered. This patient required succinylcholine and tracheal intubation. These five patients were excluded from the analysis.

Demographic variables, including age, sex, weight, surgical severity scores,³ duration of surgery, and anesthesia were similar in all groups (table 1). No adverse events such as laryngospasm or postoperative respiratory depression (respiratory rate ≤ 16), bronchospasm, or hypoxemia were noted from the study drug administration.

The frequency of agitation scores of 3 and 4 were significantly decreased with nasal fentanyl regardless of inhalation agent used. (35/130 vs. 78/130; *P* < 0.05). The incidence of severe postoperative agitation (agitation score of 4) was significantly less when intranasal fentanyl was administered, regardless of the inhalation anesthetic used (2/130 vs. 22/130; *P* < 0.05; table 2). Similarly, the maximum postoperative heart rate, agitation, and CHEOPS scores were significantly decreased with the use of intranasal fentanyl regardless of the use of halothane or sevoflurane. The times from arrival in the PACU to discharge readiness and actual discharge from phase 1 PACU were increased if fentanyl was administered. However, the use of fentanyl was not associated with an increase in the duration of stay in the phase 2 PACU or in the total time from the end of surgery to discharge readiness and actual discharge from hospital (tables 1 and 2). In addition, there were no differences in the time from the end of the surgical procedure to

Table 2. Recovery Data

	Sevoflurane + Nasal Fentanyl	Sevoflurane + Nasal Placebo	Halothane + Nasal Fentanyl	Halothane + Nasal Placebo
N	64	69	66	61
Number (%) with severe agitation	1 (2%)*	16 (23%)	1 (2%)*†	6 (10%)
Maximum agitation score				
Median (interquartile range)	1 (0–3)*	3 (2–4)	1 (0–2)*†	3 (1–4)‡
Mean ± SD	1.8 ± 0.9*	2.7 ± 1.0	1.6 ± 0.9*†	2.4 ± 1.0‡
Maximum CHEOPS score				
Median (interquartile range)	6 (4–8)*	9 (6–12)	6 (4–8)*†	8 (4–12)‡
Mean ± SD	7.3 ± 1.6*	8.6 ± 1.8	7.0 ± 1.5*†	8.4 ± 1.9‡
Maximum heart rate (beats/min)	139 ± 15*	148 ± 19	134 ± 19*†	149 ± 21‡
Time from arrival to discharge readiness (min)				
From phase 1 PACU	28 ± 21*	17 ± 14	30 ± 18*†	23 ± 20
Enter phase 2 to exit phase 2 PACU	31 ± 21	36 ± 18	32 ± 20	33 ± 16
Time from arrival to actual discharge (min)				
From phase 1 PACU	36 ± 20*	26 ± 15†	39 ± 16*	34 ± 18
Enter phase 2 to exit phase 2 PACU	44 ± 23	53 ± 23	49 ± 33	48 ± 27

* *P* < 0.05 versus sevoflurane–placebo group. † *P* < 0.05 versus halothane–placebo group. ‡ *P* < 0.05 versus sevoflurane–fentanyl group. CHEOPS = Children’s Hospital of Eastern Ontario Pain Scale; PACU = postanesthesia care unit.

discharge readiness and actual discharge from phase 1 and phase 2 of the PACU and from the hospital. The incidence of postoperative emesis in hospital, at home, and during the entire 24-h postoperative period was not increased with the use of fentanyl (table 3). Nurses in both phases 1 and 2 PACU had higher levels of satisfaction with patient behavior in children who received intranasal fentanyl. However, overall parental satisfaction with anesthetic care, which was assessed 24 h after the procedure, did not differ between the four groups.

The incidence of severe postoperative agitation did not differ in placebo-treated patients who underwent anesthesia with halothane or sevoflurane. There were no significant differences in the postoperative maximum heart rate, CHEOPS and agitation scores, times to discharge readiness and actual discharge, and nurses and parent satisfaction assessments in patients who received halothane or sevoflurane. The incidence of emesis while the child was in hospital did not differ significantly between any of the four groups. However, the incidence of emesis at home and during the entire first postoperative 24 h were significantly higher in patients who received halothane.

Discussion

This study demonstrates that the administration of fentanyl by the intranasal route decreased the incidence of severe emergence agitation without increasing postoperative respiratory depression, emesis, or discharge from the hospital in children undergoing BMT procedures. Because this operation is usually performed without intravenous access, options for providing analgesia and sedation in the PACU are limited. It is difficult to establish vascular access and impractical to use the oral route of drug administration in a combative, disoriented child who is thrashing around. The absorption of drugs administered rectally is too erratic and slow in these patients. Prophylactic therapy has obvious advantages, but the drugs used should be effective, with minimal side effects, given by a route that should be acceptable to the child and economical.

Prophylactic acetaminophen and nonsteroidal anti-inflammatory drugs such as ibuprofen and ketorolac have been administered orally in the preoperative period to provide for postoperative analgesia in this patient population. Preoperative oral acetaminophen 10–15 mg/kg

Table 3. Postoperative Complications and Satisfaction Scores

	Sevoflurane + Nasal Fentanyl	Sevoflurane + Nasal Placebo	Halothane + Nasal Fentanyl	Halothane + Nasal Placebo
N	64	69	66	61
Postoperative emesis (n [%])				
In hospital	12 (19%)	9 (13%)	18 (27%)	12 (20%)
After discharge	19 (30%)	15 (22%)	34 (52%)*	30 (49%)*
During first 24 h	21 (33%)	20 (29%)	34 (52%)*	32 (52%)*
Satisfaction scores provided by:				
Phase 1 PACU nurse (VAS [mm])	82 ± 25†	53 ± 36	85 ± 25†‡	61 ± 37*
Phase 2 PACU nurse (VAS [mm])	77 ± 25†	55 ± 31	80 ± 25†‡	62 ± 36*
Parents (0–10)	9.8 ± 0.6	9.3 ± 1.9	9.5 ± 1.7	9.2 ± 1.7

* *P* < 0.05 versus sevoflurane–fentanyl group. † *P* < 0.05 versus sevoflurane–placebo group. ‡ *P* < 0.05 versus halothane–placebo group. PACU = postanesthesia care unit; VAS = visual analog scale.

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and ibuprofen 10 mg/kg have not been shown to be more effective than placebo, but ketorolac 1 mg/kg by the oral or intravenous route reduced the incidence of postoperative agitation after BMT. However, ketorolac may not be completely effective, as 12–30% of patients still required rescue analgesics.

Previous studies have also examined the efficacy of opioids in preventing postoperative agitation.^{2,5} The preoperative administration of oral codeine 1 mg/kg with acetaminophen 10 mg/kg provided superior analgesia compared with oral acetaminophen 15 mg/kg in this patient population.⁵ Butorphanol, a synthetic opioid agonist–antagonist, has also been administered by the transnasal route, but is effective only in a dose of 25 $\mu\text{g}/\text{kg}$.² It is unclear if the improvement in postoperative behavior after prophylactic opioid therapy reflects better analgesia or greater sedation. The need for rescue therapy in the PACU after preoperative oral ketorolac may be a reflection of inadequate sedation or analgesia.^{3,12,16}

Both ketorolac and butorphanol are relatively expensive drugs, and the use of these to achieve only a slight improvement in analgesia may not be cost-effective, given the large number of BMT procedures performed in this country.^{2,16} Fentanyl is an inexpensive generic synthetic opioid, and intranasal administration avoids the costs of equipment and time taken to establish vascular access in all children who undergo BMT, an operation that typically takes less than 10 min to perform. Intranasal administration of fentanyl immediately after induction avoids the need for patient cooperation without causing clinically important delays in the onset of action.

Gourlay *et al.*²⁶ studied adults who received fentanyl by patient-controlled analgesia after intra-abdominal procedures. These investigators noted that the minimum effective concentration for analgesia was 0.63 ± 0.25 ng/ml (mean \pm SD). There are no similar data available for the pediatric patient population. The mean serum fentanyl concentrations that we determined in the first phase of our study equaled or exceeded these values at both time points. However, conclusions regarding the relation between postoperative behavior and blood concentrations of fentanyl should not be based on the data obtained in our study and would require a more extensive dose–response curve with a larger number of patients. The values from the adult fentanyl patient-controlled analgesia study represent steady state concentrations, unlike the values from our study.²⁶ Finally, it is still unclear if the blood concentrations of fentanyl required to prevent postoperative agitation should be adequate to provide analgesia or only sedation.

There are concerns that the routine use of intranasal fentanyl in the BMT patient population will be associated with increased side effects such as prolonged emergence, emesis, respiratory depression, and laryngospasm. Although the use of fentanyl prolonged the duration of stay in phase 1 PACU by 7–10 min, the time

from the end of surgery to arrival in the PACU and to the time patients were ready to be discharged and actually discharged from hospital did not differ between the study groups. The use of fentanyl did not increase intraoperative laryngospasm, postoperative emesis, oxygen requirements in the PACU, or the incidence of hypoventilation (respiratory rates ≤ 16 breaths/min) in our study. However, we studied only healthy patients, and the dose of fentanyl may need adjustment in children with ASA physical status III and IV, particularly if they have impaired respiratory control and airway obstruction (*e.g.*, children with developmental delay or abnormal airways). We also did not note any clinically important changes in ventilatory compliance after nasal fentanyl 2 $\mu\text{g}/\text{kg}$, but this has been reported in children receiving nasal sufentanil, 4.5 $\mu\text{g}/\text{kg}$, for preanesthetic sedation.¹ Larger studies may be needed to show significant differences in the incidence of infrequent events such as laryngospasm, chest wall rigidity, and upper airway obstruction when nasal fentanyl is administered during sevoflurane or halothane anesthesia.

Sevoflurane, a potent inhalation agent with low blood gas solubility, has become very popular in pediatric anesthesia because it provides a rapid, smooth induction, a faster emergence, and is associated with decreased cardiac depression compared with halothane.⁷ decreased incidence of emesis with sevoflurane compared with halothane was noted in our study and another study of children undergoing ear–nose–throat surgery, but is not a consistent finding in all studies comparing these inhalation agents.^{7,8,13,27} There are more consistent reports of increased agitation on emergence after sevoflurane,^{4,7} even if adequate postoperative analgesia was provided by a regional block.^{6,8} Very rapid emergence from anesthesia may not be as desirable in children compared with adults, particularly if associated with increased emergence agitation. The benefits gained in improved operating-room efficiency from 2–3 min earlier awakening are lost because a combative, disoriented child requires additional nursing care in the PACU to prevent self-injury.

Our study also demonstrated that the use of sevoflurane was not associated with increased postoperative agitation compared with halothane when nasal fentanyl was used (2% for both groups). These results are in agreement with other investigations in children who received midazolam during BMT procedures.^{3,13} However, in other studies the incidence of agitation on emergence was higher with sevoflurane in BMT patients who did not receive preanesthetic medication with midazolam and in patient populations undergoing other procedures.^{4,7} It is possible that a larger study would have detected a statistically significant difference in the rates of emergence agitation in the placebo groups (23% *vs.* 10% for sevoflurane and halothane, respectively; $P = 0.06$).

In conclusion, this study has shown that the administration of fentanyl, 2 µg/kg by the intranasal route, results in serum concentrations that are associated with adequate analgesia in adults. The intranasal administration of fentanyl was associated with decreased agitation in the PACU, decreased CHEOPS scores, a slightly longer stay in the phase 1 PACU, and greater satisfaction among the PACU nurses caring for the child. There were no differences in the total hospital stay or in the incidence of postoperative emesis, respiratory depression, and oxygen requirements. Postoperative agitation, CHEOPS pain scores, and duration of hospital stay did not differ in patients receiving halothane or sevoflurane. Anesthesiologists should consider the use of nasal fentanyl in children undergoing BMT procedures.

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