

# Efficacy of Addition of Fentanyl to Epidural Bupivacaine on Postoperative Analgesia after Thoracotomy for Lung Resection in Infants

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**Background:** The authors evaluated the efficacy of adding fentanyl to epidural bupivacaine in infants up to 6 months of age after a thoracotomy in a prospective, randomized, double-blind study. The primary outcome was the total amount of rescue doses of intravenous nalbuphine in the first 24 h after surgery. Secondary outcomes included (1) time to first rescue dose of nalbuphine, (2) pain scores, and (3) behavior scores.

**Methods:** Thirty-two infants were randomly assigned to receive an epidural infusion containing 0.1% bupivacaine (group B; n = 16) or 0.1% bupivacaine and 2 µg/ml fentanyl (group BF; n = 16). Patients were evaluated up to 24 h after surgery for pain; amount of analgesic rescues and time to first rescue; pain scores; behavior scores (five-item behavior score); and complications, including respiratory depression, oxygen requirement, vomiting, and urinary retention.

**Results:** The two groups had similar demographics. Nalbuphine consumption ( $P = 0.001$ ) and pain scores ( $P < 0.001$ ) in the first 24 h were significantly decreased in group BF compared with group B. The time to first analgesic rescue was significantly longer in group BF ( $P = 0.005$ ). The five-item behavior score was significantly better in group BF than in group B ( $P = 0.01$ ). The incidence of side effects, the time to first successful feeding, and the time to discharge were similar in both groups.

**Conclusions:** Addition of 2 µg/ml epidural fentanyl to 0.1% bupivacaine results in improved postthoracotomy analgesia without any increase in side effects, compared with 0.1% bupivacaine, in infants up to 6 months of age.

CONGENITAL cystic lung lesions and other intrathoracic conditions may require a thoracotomy and resection in the first few months of life.<sup>1</sup> The use of a thoracic epidural catheter for intraoperative and postoperative analgesia in neonates and infants<sup>2-6</sup> offers the advantage of minimizing the use of intravenous opioids,<sup>7</sup> which can cause, particularly in this population, apnea, bradycardia, and, occasionally, respiratory arrest.<sup>8</sup> Data on the efficacy and safety of epidural opioids in neonates is limited and often contradictory. Old reports based on a limited number of patients have shown that epidural

opioids can be safely administered in infants.<sup>4,5</sup> However, other studies have reported complications such as severe respiratory depression from the use of epidural opioids.<sup>9-12</sup> Furthermore, a recent retrospective study questioned the safety and benefits of adding fentanyl to epidural bupivacaine.<sup>13</sup> No randomized studies have been conducted to address these controversial issues in infants.

In this prospective, randomized, double-blind study, we assessed whether the addition of fentanyl to epidural bupivacaine improves the quality of postoperative analgesia and accelerates the clinical recovery of infants after thoracotomy. The primary outcome was to determine the total number of rescue doses of intravenous nalbuphine received by the patients in the first 24 h after the operation. Secondary outcomes measured included (1) duration of analgesia, measured as the interval between the end of the operation and the first rescue dose of nalbuphine; 2) pain scores; and 3) comfort level using the five-item behavior score.<sup>14</sup>

## Materials and Methods

This prospective, randomized, double-blind study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Written informed consent was obtained from the parents of all children.

Full-term infants, aged 0-6 months, with American Society of Anesthesiologists physical status I-III, scheduled to undergo a thoracotomy for lung resection or resection of bronchopulmonary sequestration and whose postoperative plan included continuous epidural analgesia, were included in this study. Before their arrival in the operating room, study patients were randomly assigned using computer-generated random numbers (in blocks of four) to receive a continuous epidural infusion of a solution containing 0.1% bupivacaine alone (group B) or 0.1% bupivacaine and 2 µg/ml fentanyl (group BF).

Exclusion criteria included intubation before arrival in the operating room and known allergies to any of the medications used in the study. The study was terminated if the epidural catheter could not be placed, the tip of the catheter was not at a T5-T10 level, adequate postoperative analgesia could not be provided within the study parameters, or the patient could not be extubated in the operating room at the end of the

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procedure. The study was conducted between June 2005 and December 2007.

#### *Anesthetic Technique*

On arrival in the operating room and after placement of appropriate monitors (continuous pulse oximetry, electrocardiography, and blood pressure recorded every 3 min), general anesthesia was induced with sevoflurane in oxygen. Neuromuscular blockade was obtained with 0.1 mg/kg vecuronium, and the trachea was intubated. Anesthesia was maintained with desflurane in oxygen and air. Additional doses of intravenous vecuronium (0.05 mg/kg) were administered as needed.

#### *Study Protocol*

The study epidural infusion (group B or group BF) was prepared by the pharmacist according to the computer-generated randomization and was then delivered to the operating room. Randomization was performed in blocks of four.

The epidural catheter was placed under sterile conditions through a caudal or a lumbar approach after intubation. The catheter was advanced in the epidural space to the mid-thoracic level (T5–T10), and the position of the tip was confirmed radiologically with contrast (Omnipaque 180; GE Healthcare, Princeton, NJ) (as per protocol in every patient receiving a caudal catheter at our institution). A test dose (0.08 ml/kg) of 1.5% lidocaine with 1:200,000 epinephrine was administered through the epidural catheter. After the test dose, an initial bolus of 0.5 ml/kg bupivacaine, 0.25%, was administered,<sup>15</sup> and immediately after, the infusion of the study epidural solution was started at a rate of 0.25 ml · kg<sup>-1</sup> · h<sup>-1</sup> using a CADD Prizm PCS II pump (model 6101; Smith Medical MD, Inc., St. Paul, MN). Inadequate intraoperative pain relief (heart rate and blood pressure > 20% from the basal value) was managed by increasing the concentration of inspired desflurane. No opioids or ketorolac was administered intraoperatively.

#### *Postoperative Period*

At the end of the procedure, residual neuromuscular blockade was reversed, and the trachea was extubated. Infants were then transferred to the neonatal intensive care unit (NICU) for monitoring of cardiovascular and respiratory parameters until hospital discharge.

Inadequate postoperative analgesia, defined as a CRIES (Crying, Requires oxygen for saturation < 95%, Increased vital signs, Expression, Sleepless) score of 4 or greater,<sup>16</sup> was initially managed with 0.05 mg/kg intravenous nalbuphine every 4 h as needed. In case of persistent increased pain scores, 0.5 mg/kg intravenous ketorolac was then administered every 6 h until patients were comfortable. If an inadequate sensory level (tested by pinching the skin on physical examination)<sup>17</sup> was noted, a bolus of 1 ml lidocaine, 1%, was administered

through the epidural catheter, and the epidural infusion rate was then increased to 0.3 ml · kg<sup>-1</sup> · h<sup>-1</sup>. If pain persisted despite these measures, the epidural study infusion was stopped and replaced with a 0.1% bupivacaine solution and an intravenous infusion of morphine at an initial rate of 0.02 mg · kg<sup>-1</sup> · h<sup>-1</sup>. Patients who did not void urine after 8 h had their bladder catheterized. Feeding was initiated when the child was awake enough to be fed, had a soft abdomen, and had positive bowel sounds.

#### *Study Parameters*

All personnel involved with the intraoperative and postoperative care of the patient were blinded to the patient's group assignment, and only the pharmacist was aware of the randomization code. The evaluation started as soon as the patient arrived at the NICU after surgery, which was designated as time 0. The primary endpoint was the total amount of intravenous nalbuphine administered in the first 24 h postoperative period. The parameters observed included the following:

1. Hourly vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation).
2. Pain assessment by the nursing staff using the CRIES pain scale,<sup>16</sup> which ranges from 0 to 10. This was measured at 0, 1, 4, 8, 12, 16, 20, and 24 h (time 0 corresponded to time of arrival at the NICU).
3. Number of intravenous rescue medications administered in the first 24 h, any additional epidural catheter boluses, and increases in epidural infusion rate.
4. Time to the first analgesic rescue dose. If the patients received no rescue in the first 24 h, the time to first rescue was considered as 24 h for statistical purposes.
5. Time to the first successful feeding (defined as acceptance of a regular oral feeding—formula or breast milk—without vomiting) after the operation.
6. Behavior score using the five-item behavior score<sup>18</sup> every 4 h. Each of the five items was scored as 0 or 1. Items were as follows: facial expression—calm and relaxed (0) or pronounced (1); sucking—absent (0) or strong and rhythmic with a pacifying effect (1); spontaneous motor activity—normal (0) or agitated (1); excitability, responsiveness to stimulation—normal (0) or tremulous, clonic movements (1); and excessive flexion (fingers and toes)—absent (0) or present and constant (1). Infants who had a total score of 0 or 1 were judged to have satisfactory behavior.<sup>18</sup>
7. Complications, including respiratory depression (apnea lasting at least 20 s or apnea of any duration associated with heart rate < 100 beats/min, oxygen saturation < 90%, or cyanosis), need for intervention (controlled ventilation with bag and mask, reintubation, supplemental oxygen and/or naloxone administration), and urinary retention (requiring bladder

catheterization), were recorded. The respiratory rate was measured continuously *via* the electrocardiographic leads and hourly by the nursing staff by physical examination. The lower limit for the cardiorespiratory alarms was set as follows: pulse oximetry, 90%; heart rate, 100 beats/min; and respiratory rate, 20 breaths/min. The apnea alarm time was set at 15 s.

### Statistical Analysis

The sample sizes were based on the primary outcome measures involving the amount of intravenous nalbuphine used in the 24 h after admission into the recovery room. We hypothesized a reduction in the use of intravenous nalbuphine of 50% from  $400 \pm 200$  to  $200 \pm 130$   $\mu\text{g}/\text{kg}$  per 24 h, based on data observed in infants previously treated at The Children's Hospital of Philadelphia. We calculated that 12 patients would be required in each of the two groups to demonstrate a 50% difference in the consumption of intravenous nalbuphine in the first 24 h after thoracotomy at a level of significance of  $P = 0.05$  and a power of 80%. We recruited 16 subjects per group (total 32 infants for two groups) to account for an expected attrition rate of 25%.

The demographic differences between the two groups were assessed by using *t* tests for the continuous variables (age, weight, duration of surgery) and the chi-square test for categorical data (sex). Pain intensity (CRIES scores) was compared between the two groups at different time points using one-way repeated-measures analysis of variance with a series of *t* tests to examine responses over time, followed by the Tukey multiple comparison test when differences between mean values were observed. Nonparametric methods were used when the numerical and ordinal data did not have normal distributions according to the Shapiro-Wilk test of normality (Kruskal-Wallis and Mann-Whitney U test). The log-rank test was used to analyze the difference between the two groups with respect to the time to first dose of rescue medication. Data are presented as mean  $\pm$  SD unless otherwise specified.

The statistical analysis was conducted using Stata/SE 8.2 (StataCorp, College Station, TX).

## Results

A total of 32 patients (16 in each group) were enrolled, and everyone completed the study. The two groups were similar with respect to their demographics and type of surgical procedure (table 1). Age distribution was as follows: 0–30 days (BF: 1, B: 0), 31–60 days (BF: 7, B: 10), 61–90 days (BF: 6, B: 3), and greater than 90 days (BF: 2, B: 3). Two children were born preterm (1 in each group). One patient (group B) was born at 34 weeks' gestation with a postconceptual age of 49 weeks, and another (group BF) was born at 35 weeks' gestation with a postconceptual

**Table 1. Demographic and Intraoperative Data**

Parameter	Group BF, n = 16	Group B, n = 16	P Value
Age, days	67 $\pm$ 26	66 $\pm$ 52	0.48
Sex, M/F	7/9	9/7	0.48
Weight, kg	5.1 $\pm$ 1	4.8 $\pm$ 1.3	0.22
Location of the tip of the epidural catheter, range	T5–T9	T6–T10	0.2
Duration of surgery, min	105 $\pm$ 57	109 $\pm$ 36	0.43
Procedure			
Lower lobectomy	12	13	
Upper lobectomy	0	1	
Middle lobectomy	1	0	1
Removal of bronchopulmonary sequestration	3	2	
Level of incision			
Fifth intercostal space	15	16	1
Sixth intercostal space	1	0	

Group B = 0.1% bupivacaine; group BF = 0.1% bupivacaine and 2  $\mu\text{g}/\text{ml}$  fentanyl.

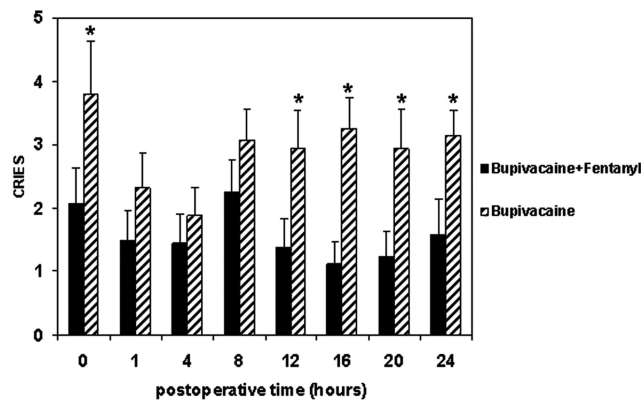
age of 42 weeks. None of the patients had any significant symptoms related to their intrathoracic condition.

### Analgesic Use

After admission to the NICU, 24-h nalbuphine consumption was significantly reduced (44%) in group BF. The total nalbuphine consumption in the first 24 h was  $121.9 \pm 91.2$   $\mu\text{g}/\text{kg}$  in group BF and  $218.8 \pm 77.2$   $\mu\text{g}/\text{kg}$  in group B ( $P = 0.001$ ). The time to first analgesic rescue was significantly longer ( $P = 0.005$ ) in group BF ( $516 \pm 524$  min) than in group B ( $126 \pm 89$  min). The total ketorolac consumption was  $0.7 \pm 0.7$  mg in group BF and  $1 \pm 0.7$  mg in group B ( $P = 0.08$ ).

### Pain Score

Patients in group BF experienced significantly less pain than those in group B. The CRIES score in the first 24 h was significantly decreased in group BF ( $1.5 \pm 1.9$ ) when compared with group B ( $2.9 \pm 2.3$ ) ( $P < 0.001$ ). Figure 1 demonstrates the pain scores at different time intervals in the first 24 h.



**Fig. 1.** Box plot showing mean CRIES (Crying, Requires oxygen for saturation  $< 95\%$ , Increased vital signs, Expression, Sleepless) pain scores with SE bars. \*  $P < 0.05$ .

### Other Parameters

The five-item behavior score (a score of 0 or 1 suggests a calm child) was significantly better in group BF ( $1 \pm 0.7$ ) than in group B ( $1.9 \pm 1.3$ ) ( $P = 0.01$ ). No significant differences were observed between the two groups ( $415 \pm 285$  min in group BF vs.  $389 \pm 349$  min in group B) with respect to time to the first successful feeding ( $P = 0.41$ ). The time to discharge among patients who had no surgical complications was similar in the two groups (median, 2 days; range, 2–4 days;  $P = 0.43$ ). Two patients in group BF had persistent pneumothoraces due to continuing leakage and were discharged on days 9 and 16.

Four patients in group B received one lidocaine bolus each, whereas one patient in group BF received a lidocaine bolus ( $P = 0.33$ ). The amount of bupivacaine used in 24 h was  $61.9 \pm 3.7$  mg/kg in group B and  $60.8 \pm 3.0$  mg/kg in group BF ( $P = 0.35$ ).

Two patients in each group had to have their bladder catheterized once for urinary retention. No respiratory events necessitating assisted ventilation or administration of naloxone occurred in either group.

## Discussion

This study demonstrates that the addition of fentanyl to bupivacaine in the epidural infusion provides superior analgesia during the first 24 h postoperative period when compared with bupivacaine alone in infants undergoing thoracotomy for lung resection.

The efficacy and safety of epidural opioids have been extensively studied in adult patients with randomized clinical trials. The safety of epidural opioids has also been demonstrated in infants and neonates when vital signs are continuously monitored in the postoperative period.<sup>19</sup> Several authors have questioned the validity of these data because they came from retrospective studies. To further complicate the issue, the authors of a recent study have questioned the clinical advantages of adding fentanyl to the local anesthetic in infants. In this report, children who received an epidural infusion of bupivacaine (1 mg/ml) and fentanyl (2–5  $\mu$ g/ml) had a longer hospital stay, more frequent episodes of respiratory depression, and no obvious advantages in analgesia level compared with infants who received epidural bupivacaine (1 mg/ml) alone.<sup>13</sup> However, this report has several limitations, which include a retrospective design, a nonuniform method of pain assessment and rescue analgesic administration, use of a wide range (2–5  $\mu$ g/ml) of fentanyl, and lack of information on the position of epidural catheters.

In our study, the addition of fentanyl to the epidural infusate did not have any significant effect on the infants' recovery from surgery and did not delay their return to normal feeding or discharge from the hospital. Also, the

incidence of the most common side effects caused by epidural opioids (respiratory depression and urinary retention) was similar in both groups of patients. Delayed respiratory depression after administration of epidural opioids in infants and young children has been reported in the past.<sup>9–12</sup> However, these reports are associated with the use of high-dose morphine in the epidural space, and not fentanyl. In addition, most of these episodes of respiratory depression have been observed in infants who received supplemental intravenous opioids.<sup>19</sup>

The addition of a low dose of fentanyl to the epidural infusion in this group of patients decreased the need for intravenous rescue medications and offered a longer pain-free interval from the time of administration of the initial epidural bolus. The importance and advantages of providing adequate perioperative analgesia in infants and neonates have been well described.<sup>14,20,21</sup> These include minimizing the endocrine and metabolic responses associated with surgical stress and decreasing the risk of neurobehavioral changes later in childhood.<sup>22–26</sup> Patients undergoing thoracotomy for lung resection usually experience severe postoperative pain and would benefit from an effective postoperative analgesic regimen.

It has been shown that it is necessary to use higher infusion rates to obtain adequate analgesia when using epidural infusions that contain local anesthetic only.<sup>27</sup> Particular attention must be paid to the infusion rates used in neonates and young infants to prevent local anesthetic toxicity.<sup>28–30</sup> The following maximum epidural infusion rates for bupivacaine have been recommended:  $0.4\text{--}0.5$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> in older infants and  $0.2\text{--}0.25$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> in neonates.<sup>29</sup> The same author has also suggested that children may not report the classic symptoms of central nervous system toxicity as adults do and may only manifest symptoms such as restlessness or agitation. The addition of opioids to local anesthetics in epidural infusions has been recommended to diminish the doses and toxicities of either drug.<sup>29</sup> In our study, however, no significant reduction in the amount of local anesthetic administered was noted in group BF.

We observed that patients who received epidural fentanyl, in addition to experiencing less pain, also had improved behavior scores. A score of 0 or 1 is considered to be ideal behavior and reflects a relaxed, quiet, and comfortable child. Although originally used in mechanically ventilated neonates,<sup>18</sup> this scoring method gives a global measurement of the level of pain and stress experienced by neonates.

In the study design, we purposefully did not extend the analysis beyond the initial 24 h after the operation because most of the chest tubes are usually removed (approximately 70% of infants who undergo lung resections) within 24 h from surgery at our institution and patients are discharged home on postoperative day 2. It

is our practice to remove the epidural catheter immediately after removal of the chest tube.

Although serious adverse events were not noted in this study, the sample size is inadequate to reliably estimate the risk of rare adverse events. Also, all patients in this study were monitored in the NICU (which is the standard of care at our institution for patients undergoing thoracotomy in this age group), and caution must be exercised if these patients are to be discharged to the regular floors. If these patients are discharged to the regular floors, increased vigilance needs to be exercised, in addition to appropriate monitoring, which should include continuous pulse oximetry, electrocardiography, and apnea monitoring. In addition, the small number of ex-preterm infants and infants younger than 30 days in this study limits the generalization of our conclusions to this specific population. The mean amount of fentanyl administered *via* the epidural space in group BF was  $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . The beneficial effects of the addition of fentanyl noted in this study may not be an epidural effect at all and could potentially be achieved by any type of continuous intravenous opioid administration at a similar dose. Future studies must be performed to address this issue. However, the epidural route offers the convenience of a single route of administration for both the local anesthetic and the opioid, particularly in young infants, where obtaining additional intravenous access may be difficult.

In conclusion, this prospective, randomized, double-blind study indicates that addition of  $2 \mu\text{g}/\text{ml}$  fentanyl to  $0.1\%$  bupivacaine results in improved analgesia after thoracotomy when compared with  $0.1\%$  bupivacaine alone administered epidurally in infants up to 6 months of age.

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