

# Efficacy, Safety, and Pharmacokinetics of Levobupivacaine with and without Fentanyl after Continuous Epidural Infusion in Children

## A Multicenter Trial

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**Background:** Levobupivacaine, the levo-enantiomer of bupivacaine, is as potent as bupivacaine but less toxic. Therefore, the authors investigated the efficacy, safety, and pharmacokinetics of perioperative epidural levobupivacaine with and without fentanyl in children.

**Methods:** After Research Ethics Board approval and informed written consent, 120 healthy children aged 6 months to 12 yr who were scheduled to undergo urologic or abdominal surgery were randomized in a double-blinded and concealed manner to receive one of four epidural solutions as a continuous infusion for 24 h: 0.125% levobupivacaine; 0.0625% levobupivacaine; 1  $\mu$ g/ml fentanyl; or the combination, 0.0625 levobupivacaine and 1  $\mu$ g/ml fentanyl. After induction of anesthesia and tracheal intubation, a lumbar epidural catheter was sited, a loading dose was administered (0.75 ml/kg levobupivacaine, 0.175%), and the epidural infusion was commenced. The primary endpoint was the need for rescue analgesia (morphine) in the first 10 h after surgery. Pain, motor strength, and side effects were recorded for 24 h. Venous blood was collected from 18 children to determine the plasma concentrations of levobupivacaine and/or fentanyl before and 2, 4, 8, 16, 24, and 26 or 30 h after the start of the epidural infusion.

**Results:** Of the 114 children who were analyzed for intention to treat, a similar number of children in each group reached the 10-h mark. The time to the first dose of morphine in the first 10 h was less in the plain fentanyl group ( $P < 0.044$ ). All other effects were similar among the four groups. The plasma concentration of levobupivacaine increased during the infusion period, reaching a maximum of  $0.76 \pm 0.11$   $\mu$ g/ml in the 0.125% group and  $0.48 \pm 0.12$   $\mu$ g/ml in the 0.0625% group by 24 h. The plasma concentration of fentanyl also increased steadily, reaching a maximum concentration of  $0.37 \pm 0.11$  ng/ml by 24 h.

**Conclusion:** We conclude that 0.0625% levobupivacaine without fentanyl is an effective perioperative epidural solution in children when infused at a rate of  $0.3$  ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>. The plasma concentrations of 0.125% and 0.0625% levobupivacaine and fentanyl (1  $\mu$ g/ml) at the end of a 24-h infusion are low.

ALTHOUGH bupivacaine is commonly used for continuous perioperative epidural analgesia in infants and children,<sup>1-3</sup> rare but potentially fatal toxic events have occurred. These events were either acute cardiovascular reactions from inadvertent intravascular or intraosseous injections of bupivacaine<sup>4,5</sup> or neurologic reactions from the insidious accumulation of toxic or near-toxic concentrations of bupivacaine after prolonged infusions of relatively large doses of bupivacaine.<sup>6,7</sup> Several strategies have been proposed to attenuate the risk of toxicity from bupivacaine, including use of the less-toxic levo-enantiomer of bupivacaine, levobupivacaine.

Preliminary evidence suggests that levobupivacaine is as potent<sup>8,9</sup> but less cardiotoxic<sup>10,11</sup> and less neurotoxic<sup>12</sup> than both dextrobupivacaine and the racemic mixture, bupivacaine. Improving the therapeutic ratio of bupivacaine by using the isolated L-isomer is relevant only if the potency of levobupivacaine is similar to the racemic mixture. To date, the clinical effectiveness of levobupivacaine in children for epidural analgesia remains to be established.

Although fentanyl is commonly used as an adjunctive agent in epidural infusions in children,<sup>1-3,13,14</sup> its pharmacology when it is administered by this route is poorly understood. The combination of 1-3  $\mu$ g/ml fentanyl and 0.1-0.125% bupivacaine is recommended for perioperative epidural analgesia in infants and children.<sup>1-3</sup> Lejus *et al.*<sup>15</sup> investigated the effectiveness of epidural fentanyl for postoperative analgesia in children and concluded that  $5$   $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  day<sup>-1</sup> epidural plain fentanyl was as effective as a single dose of  $50$   $\mu$ g/kg epidural morphine. However, the concentration of the fentanyl solution and the hourly infusion rate were not detailed. Currently, evidence-based support for the use of a fentanyl-bupivacaine combination for continuous perioperative epidural analgesia in children is weak.

To address these issues, we investigated the efficacy, safety, and pharmacokinetics of levobupivacaine when administered *via* the lumbar epidural route in children for perioperative analgesia and compared its effects with those of a levobupivacaine-fentanyl combination and plain fentanyl.

## Materials and Methods

### Subject Recruitment

After approval by the research Ethics Board at the three participating centers (Hospital for Sick Children,

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Received from the Department of Anaesthesia, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; the Sir Humphry Davy Department of Anaesthesia, Bristol Royal Hospital for Sick Children, Bristol, United Kingdom; and the Department of Anaesthesia, Royal Children's Hospital, Melbourne, Australia. Submitted for publication October 31, 2002. Accepted for publication June 27, 2003. Supported in part by a grant from Celltech, Slough, United Kingdom. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 20, 2001.

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Toronto, Canada; Bristol Royal Hospital for Sick Children, Bristol, United Kingdom; and Royal Children's Hospital, Melbourne, Australia) and the respective federal authorities in Canada, the United Kingdom, and Australia, informed written consent was obtained from the parents of 120 children, and written assent was obtained from those 8 yr of age and older who were deemed capable to participate in this study. All children were healthy (American Society of Anesthesiologists physical status 1 or 2), aged between 6 months and 12 yr, fasted, unpremedicated, and scheduled for elective urologic or abdominal surgery as inpatients for 24 h. The anticipated duration of surgery was 1–3 h. Surgery that was expected to last more than 3 h was assessed on a patient-by-patient basis. Exclusion criteria included known hypersensitivity to amide local anesthetics, fentanyl, or morphine; birth at less than 37 weeks' gestational age and postnatal age less than 1 yr at the time of the surgery; a known history of active and severe renal, hepatic, respiratory, or cardiac disease (including dysrhythmias or atrioventricular block); obesity ( $\geq 50\%$  above ideal body weight); a history of seizures or neurologic or neuromuscular disorders; a history of having received an investigational drug or vaccine within the last 28 days; the presence of a blood-clotting disorder or blood dyscrasia; refusal or inability to administer a lumbar epidural block; surgery that included nephrectomy, splenectomy, or malignancy; or any other reason considered appropriate by the local investigator.

#### Anesthetic Protocol

On arrival in the operating room, all children were monitored with an electrocardiogram, a pulse oximeter, a temperature probe, a noninvasive arterial blood pressure device, and an airway gas monitor (end-tidal isoflurane, nitrous oxide, and carbon dioxide concentrations). Peripheral intravenous access was secured after administration of nitrous oxide–oxygen with or without previous application of EMLA (AstraZeneca PLC, Wilmington, DE) or amethocaine cream to the dorsal surface of an upper extremity. After an intravenous induction of anesthesia using 2–5 mg/kg propofol and tracheal intubation with either rocuronium bromide or vecuronium bromide (0.5–1 mg/kg), anesthesia was maintained with isoflurane in 66% nitrous oxide and the balance as oxygen. The concentration of isoflurane was titrated to the child's anesthetic requirements. Neuromuscular blockade was maintained using repeated intravenous rocuronium or vecuronium intermittently throughout the procedure. After induction of anesthesia but before levobupivacaine was administered, a baseline 12-lead electrocardiogram was recorded, and a second intravenous access was established in an extremity other than the one in which the intravenous fluid was infusing. No additional pain medications or treatments were adminis-

tered. All ancillary medications (*i.e.*, antibiotics) that were administered were recorded.

After induction of anesthesia but before surgical incision, each child was positioned in the lateral decubitus position. An 18-gauge Tuohy needle was inserted into the L3–L4 or L4–L5 interspace under sterile conditions. The epidural space was identified by the loss of resistance to saline or air. Care was taken to avoid injecting air into the epidural space. A 21-gauge epidural catheter was threaded into the epidural space to a distance of 3–6 cm from the skin surface. If blood or cerebrospinal fluid was identified, the needle was reinserted one intervertebral space above or below the previous level.

During surgery, all children received at least 10–20 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> lactated Ringer's solution. At the end of surgery, neuromuscular paralysis was antagonized at the discretion of the investigator using an anticholinesterase and an anticholinergic.

#### Study Drug

When the epidural catheter was secured, a loading dose of 0.75 ml/kg (to a maximum of 20 ml) levobupivacaine, 0.175%, was administered to all children *via* the epidural catheter in small incremental volumes over 5 min. Each child was then randomized to receive one of four possible continuous infusions through the epidural catheter: 0.0625% levobupivacaine, 0.125% levobupivacaine, 1  $\mu$ g/ml fentanyl, or 0.0625% levobupivacaine with 1  $\mu$ g/ml fentanyl. The randomization sequence was computer generated by the Statistics and Data Management Department of Inveresk Research International Ltd. (Tranent, Scotland, United Kingdom) and prepared in a double-blind and concealed manner. Randomization was stratified by age (*i.e.*, block randomization was performed for children aged 6 months to 2 yr, 2 yr to under 7 yr, and 7–12 yr for each treatment group). Each epidural solution was prepared in a coded syringe that was labeled with the child's study number in the hospital pharmacy. If the child was allocated a randomization number but did not undergo surgery, then the child and the randomization assignment were replaced. Infusion of the continuous epidural solutions (volumetric rate of 0.3 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>) was commenced immediately after the loading dose of 0.175% levobupivacaine using a commercially available infusion pump and was continued for a maximum of 24 h. In the case of an emergency that was related or possibly related to the study or study drug, the pharmacist was authorized to disclose the contents of the syringe to the staff anesthesiologist.

#### Assessments

The duration of surgery, blood loss, and volume of lactated Ringer's solution infused were recorded. The time of extubation was defined as time zero of the postoperative period.

During the study period, hemodynamic variables, pain,

motor block, and the level of sedation were recorded. Heart rate and noninvasive arterial blood pressure (systolic and diastolic measurements) were recorded every 2 h after the start of the epidural infusion up to 24 h. Hypertension and hypotension were defined as a 30% increase or decrease, respectively, from baseline blood pressure. Hypertension was treated first by increasing the concentration of isoflurane and second by administering boluses of propofol. Hypotension was treated first by decreasing the concentration of isoflurane and administering 10-ml/kg intravenous boluses of lactated Ringer's solution and second by administering vasopressors. A 12-lead electrocardiogram was obtained 6 and 10 h after the start of the epidural infusion.

Pain was assessed using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) 10 min after extubation, every 10 min for the first hour, hourly for the next 8 h, and then again at 16 and 24 h after commencing the epidural infusion.<sup>16</sup> Additional assessments were made between these times if indicated. If the CHEOPS score was 6 or greater and the clinical assessment was consistent with a diagnosis of pain, rescue medication was administered and the time of administration noted. Rescue analgesia consisted of an intravenous loading dose of morphine, 50–100  $\mu\text{g}/\text{kg}$ , followed by an infusion of 10–40  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  as required. If rescue medication was required despite a functioning epidural, the study drug was continued. If morphine was ineffective, the child was withdrawn from the trial, the epidural study drug was discontinued, and the child was treated as per the investigator's standard practice. All supplemental analgesics (*i.e.*, acetaminophen, codeine, and suppositories of opium-belladonna) and other medications that were administered during the study period were recorded.

Motor block was assessed hourly using the following modified Bromage scale from the commencement of the infusion until the block had dissipated: 0 = no movement, 1 = movement without opposition, 2 = movement against gravity, 3 = sustained movement against gravity and force (*i.e.*, restricted by nurse to prevent leg raising). If the investigator judged the degree of motor blockade to be excessive, then the epidural infusion rate could be reduced by 0.1 ml/kg every hour until the motor block resolved. If the investigator could not maintain satisfactory analgesia after decreasing the epidural infusion rate, the epidural was discontinued, and rescue analgesia was administered. Irrespective of the outcome, when the epidural infusion rate was reduced, the child was withdrawn from the study but was followed up for the entire 24 h for safety data.

The primary endpoint of the study was the proportion of children who required morphine rescue analgesia in the first 10 h after the start of the epidural infusion. Three secondary endpoints were also evaluated: the proportion of children who required any rescue analgesia in

the 10 h after the start of the epidural infusion, the proportion of children who required any rescue analgesia in the 24 h after the start of the epidural infusion, and the time to first administration of morphine rescue analgesia in the first 10 h after the start of the epidural infusion.

If technical problems such as clinically significant bleeding or leaking around the epidural catheter or dislodgement of the catheter occurred and the epidural block was judged to be inadequate or unreliable postoperatively, the epidural infusion was discontinued, and rescue analgesia was administered. In this case, the child was withdrawn from the study and was not replaced.

Nausea or vomiting (two episodes in 1 h or persistent vomiting) was treated with 0.5 mg/kg dimenhydrinate or 0.1 mg/kg ondansetron intravenously. If the nausea or vomiting persisted after two doses of antiemetic medication, the child was withdrawn from the study, and the epidural infusion was changed from the study medication to 0.125% plain bupivacaine at the same infusion rate.

Postoperative assessments, recordings, and blood sampling were not performed in children who were sleeping at the designated times. All children, including those who required rescue analgesia in the first 10 h, were evaluated for safety during the 24-h observation period. All children were evaluated for side effects (including nausea, vomiting, and pruritus) and any other complications while in hospital and up to 3–7 days after the start of the epidural infusion. To collect data after discharge from the hospital, family members were contacted by telephone, by mail, or in person.

#### *Blood Sampling and Analyses*

Heparinized venous blood samples (2 ml) were collected from 24 children to determine the plasma concentrations of levobupivacaine and/or fentanyl. Blood was aspirated from an indwelling venous catheter located in an extremity other than the one with the maintenance intravenous. Eight blood samples were collected at the following times: before starting the epidural infusion; at 1 and 5 min; and at 1, 2, 6, 12, 24, and 26 or 30 h after starting the infusion. If the epidural infusion was discontinued before 24 h, venous blood samples were also collected 2 and 6 h after the infusion was discontinued. Each sample was centrifuged within 30 min of collection at 1,500g for 10 min, the plasma supernatant was pipetted into a glass vial, and the vial was stored at  $-20^{\circ}\text{C}$  until analysis.

All analyses were performed by Inveresk Pharmaceuticals in triplicate. For the analysis of levobupivacaine, levobupivacaine and an internal standard were extracted from human plasma with an organic solvent. The extracts were analyzed by liquid chromatography-mass spectrometry using a chiral high-performance liquid chromatography column. Linear calibration plots were



Table 1. Demographic Data

	0.125% Levobupivacaine (n = 27)	0.0625% Levobupivacaine (n = 29)	1 $\mu$ g/ml Fentanyl (n = 30)	0.0625% Levobupivacaine and 1 $\mu$ g/ml Fentanyl (n = 28)
Age, yr	4.4 $\pm$ 2.8	4.1 $\pm$ 2.9	4.0 $\pm$ 2.7	3.6 $\pm$ 2.5
Weight, kg	17.9 $\pm$ 6.6	17.6 $\pm$ 8.1	16.8 $\pm$ 6.7	16.5 $\pm$ 7.2
Height, cm	105 $\pm$ 20	99 $\pm$ 23	99 $\pm$ 19	99 $\pm$ 23
Sex (M/F)	15/12	17/12	19/11	15/13
Duration of surgery, h	1.74 $\pm$ 0.8	1.80 $\pm$ 0.94	1.93 $\pm$ 0.78	1.84 $\pm$ 0.95
Type of surgery				
Reimplantation of ureter	14	13	16	18
Hypospadias	11	13	13	5
Elective abdominal	2	2	0	1
Other	0	1	1	4

Data are mean  $\pm$  SD except for sex and type of surgery, which are number of children.

generated by weighted least-squares linear regression using peak area ratios from which the plasma levobupivacaine concentrations in the clinical samples were determined. The method was validated over the range 10–500 ng/ml, using 1-ml aliquots of plasma. Clinical samples were analyzed in batches of 40–50 samples, together with calibration standards and quality control standards. If the concentration of levobupivacaine in the sample exceeded the linear range of the assay, the sample was diluted with control plasma until the concentration reached the linear range. The actual concentration of levobupivacaine was then corrected using the corresponding dilution factor. The coefficient of variation was less than 15%.

Fentanyl and an internal standard were extracted from human plasma with an organic solvent and analyzed by liquid chromatography-mass spectrometry. Linear calibration plots were generated by weighted least-squares linear regression using peak area ratios from which the concentrations of plasma fentanyl in the clinical samples were determined. The method was validated over the range 0.05–10 ng/ml. The coefficient of variation was less than 15%.

#### Data Analysis and Statistics

The sample size was estimated using  $\alpha_2 = 0.05$ ,  $\beta = 0.2$ , a 33% failure rate to achieve the primary endpoint in the levobupivacaine-fentanyl group, and a 68% incidence of failure in the plain fentanyl group. Thirty children were required in each group.

*Post hoc* analysis of continuous data was achieved using one-way analysis of variance, and analysis of discrete data was achieved using the stratified log-rank and Mantel-Hansel tests. Pharmacokinetic parameters for plasma levobupivacaine and fentanyl were estimated using WinNonlin software (version 1.1; Pharsight Corp., Mountain View, CA). The concentration-time profiles were analyzed using a noncompartmental approach with WinNonlin model 200 software. A significance level of  $P < 0.05$  was accepted, and all  $P$  values were the results of two-sided tests.

#### Results

Of the 120 children who were enrolled in this study, 114 were analyzed on the basis of intention to treat. Six children were not analyzed for the following reasons: one did not receive the study medication, two only underwent exploratory surgery, and three experienced technical difficulties with the epidural.

The demographic data for the children in the four treatment groups were similar (table 1). Six children required morphine rescue analgesia within the first 10 h of the start of the epidural infusion (table 2). The incidences of morphine requirement were similar among the four treatments. The numbers of children in the four groups who required any analgesia in the first 10 and 24 h after the start of the epidural infusion were similar. The time to morphine rescue analgesia in the first 10 h in the fentanyl group was significantly less than that in the combined 0.0625% levobupivacaine-fentanyl group ( $P < 0.044$ ). Although one child in the 0.0625% levobupivacaine-fentanyl group required morphine in the first 10 h (table 2), morphine was administered because of a technical failure of the epidural, not failure of the epidural solution. Hence, the timing of the morphine dose was omitted from the analysis (table 2).

Heart rate (fig. 1), systemic blood pressure (fig. 2), CHEOPS (fig. 3), percent of children who were pain medication-free in the first 10 postoperative hours (fig. 4), and maximum motor block (fig. 5) during the 24-h epidural infusion period were similar among the four groups.

There were no adverse events attributable to the study drugs or to the epidural technique. Six serious adverse events were reported: four infections (one case of infectious mononucleosis, one surgical wound infection, one fever of unknown origin, and one urinary tract infection); one case of urinary retention; and one case of bowel adhesions that required surgical intervention. Side effects were similar among the four treatment groups (table 2). Urinary retention could not be evaluated postoperatively because most children were catheterized.

Plasma levobupivacaine and fentanyl concentrations

Table 2. Primary and Secondary Endpoints and Side Effects

	0.125% Levobupivacaine (n = 27)	0.0625% Levobupivacaine (n = 29)	1 $\mu$ g/ml Fentanyl (n = 30)	0.0625% Levobupivacaine + 1 $\mu$ g/ml Fentanyl (n = 28)
Primary endpoint: no. of children who required morphine in the first 10 h	1 (3.7%)	0	4 (13.3%)	1 (3.6%)
Secondary endpoints				
No. of children who required any analgesia in the first 10 h	5 (18%)	5 (17%)	8 (27%)	6 (21%)
No. of children who required any analgesia in the first 24 h	15 (56%)	13 (45%)	12 (40%)	11 (39%)
Time to first dose of morphine in the first 10 postoperative hours, h	3.3 (n = 1)	—*	2.9† (n = 4)	—‡
Side effects				
Nausea	4 (15%)	2 (6.9%)	2 (7.1%)	3 (10%)
Vomiting	6 (22%)	10 (34%)	9 (32%)	11 (36.7%)
Pruritus	2 (7.4%)	1 (3.4%)	2 (7.1%)	0

Data are number of children (%).

\* All children were censored, therefore, no comparison was performed. †  $P < 0.044$  compared with 0.0625% levobupivacaine plus 1  $\mu$ g/ml fentanyl. ‡ One child in this group was rescued with morphine within the first 10 h, but the morphine was required because of a technical failure of the epidural, not failure of the epidural solution.

were analyzed and plotted against time (figs. 6 and 7, respectively). The mean plasma concentrations of 0.125% (n = 5) and 0.0625% levobupivacaine (n = 10) increased steadily after starting the epidural infusion, reaching peaks by 24 h. The peak mean plasma concentration after infusion of 0.125% levobupivacaine,  $0.76 \pm 0.11$   $\mu$ g/ml, was approximately 50% greater than that after 0.0625%,  $0.48 \pm 0.12$   $\mu$ g/ml. The mean plasma concentration of fentanyl (n = 9) also in-

creased steadily, reaching a peak concentration of  $0.37 \pm 0.11$  ng/ml by 24 h.

## Discussion

In the current study, we investigated the effectiveness of three epidural solutions, 0.125% levobupivacaine, 0.0625% levobupivacaine, and 1  $\mu$ g/ml fentanyl, for peri-

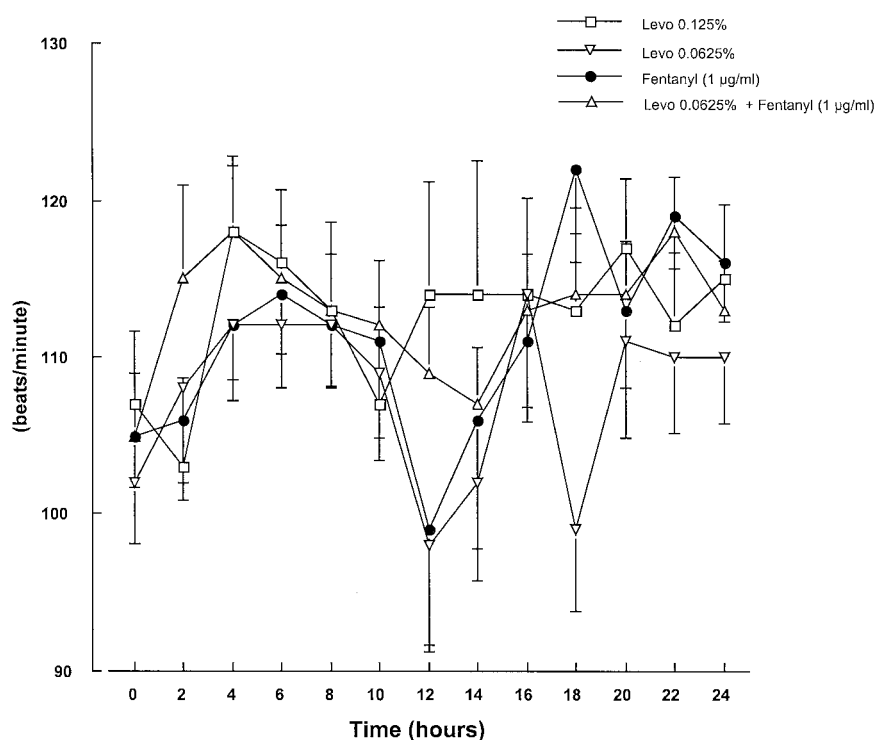


Fig. 1. Heart rate responses before and during the 24 h after the start of the epidural infusions. The mean heart rates were similar for the four treatment groups throughout the 24 h. Data are mean  $\pm$  SD. Levo = levobupivacaine.

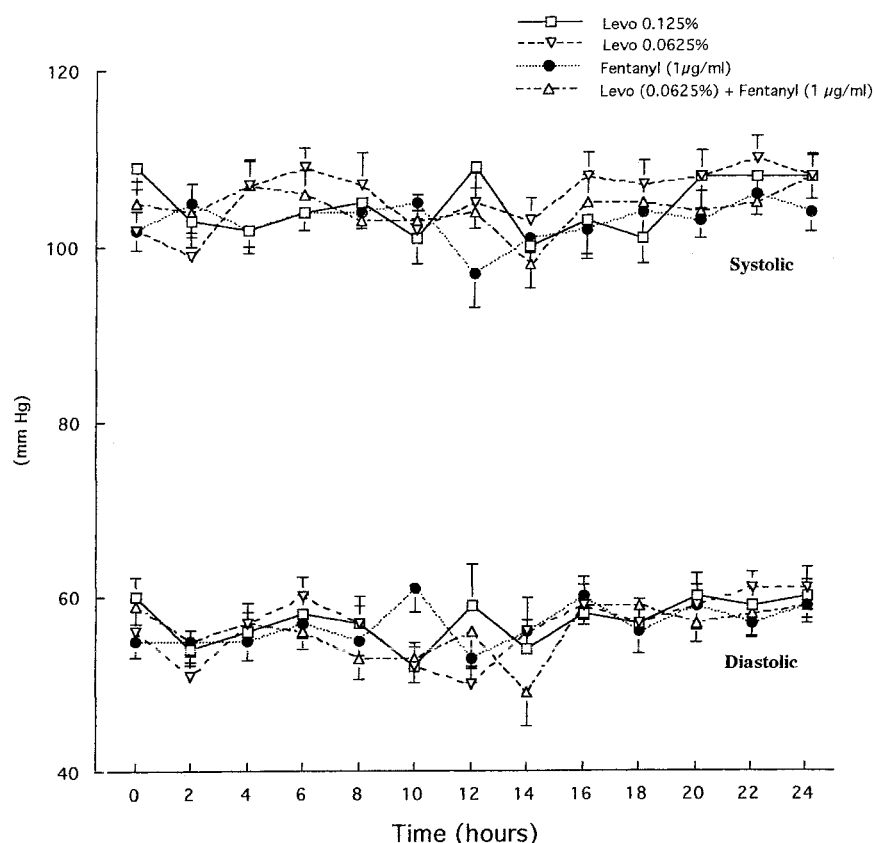


Fig. 2. Systolic and diastolic blood pressure levels before and during the 24 h after the start of the epidural infusions. Both mean systolic and diastolic pressures were similar for the four treatment groups throughout the 24 h. Data are mean  $\pm$  SD. Levo = levobupivacaine.

operative analgesia in children and compared their effectiveness with that of the combination, 0.0625% levobupivacaine and 1  $\mu$ g/ml fentanyl. The proportion of children who required rescue analgesia within the first 10 h after surgery, the primary endpoint of this study, was similar among the four treatment groups. However, the time to the first dose of rescue analgesia, a secondary endpoint, was significantly less with plain fentanyl than it was with the other three epidural solutions ( $P < 0.044$ ). These findings, together with a similar incidence of side effects (nausea, vomiting, pruritus) among the four epidural solutions, suggest that 0.125% and 0.0625% levobupivacaine and the combination 0.0625% levobupivacaine plus 1  $\mu$ g/ml fentanyl are equally effective and safe for perioperative epidural use in children for the first 24 h after urologic and abdominal surgery. In contrast, 1  $\mu$ g/ml plain fentanyl is less effective than the three levobupivacaine-containing solutions.

In designing this study, we assumed that 0.125% levobupivacaine would provide more effective analgesia (and possibly a greater incidence of side effects) than 0.0625% levobupivacaine to construct a dose response in children. Because of the dearth of clinical data with levobupivacaine in children, these assumptions were based on our clinical experience with bupivacaine. In the case of epidural bupivacaine, concentrations less than 0.1% are commonly supplemented with an opioid in children because of incomplete analgesia with con-

centrations of less than 0.1% plain bupivacaine.<sup>1</sup> However, in this study, 0.0625% levobupivacaine was as effective as 0.125% when administered as the sole epidural analgesic for 24 h after lower abdominal and urologic surgery. We attribute the effectiveness of 0.0625% levobupivacaine in this study to its potency and clinical pharmacokinetic effects.

Published studies indicate that levobupivacaine is as potent as the racemate bupivacaine.<sup>8,9</sup> Although clinical experience indicates that dilute concentrations of bupivacaine, 0.1% or less, do not provide reliable perioperative epidural analgesia in children, the results of the current study demonstrate that 0.0625% levobupivacaine is effective. This suggests that the analgesic efficacy of epidural levobupivacaine in children may be somewhat greater than the racemate bupivacaine. Alternatively, this observation may also be attributable to a type II statistical error because the sample size of the 0.125% levobupivacaine group was small, 29 children. To establish the effectiveness of and role for dilute concentrations of levobupivacaine in children, a direct comparison between epidural levobupivacaine and bupivacaine is warranted.

To optimize the pharmacokinetics of epidural levobupivacaine and fentanyl, we commenced the continuous epidural infusion immediately after the loading dose of 0.175% levobupivacaine. For reasons that remain unclear, this is neither widely recommended in the lit-

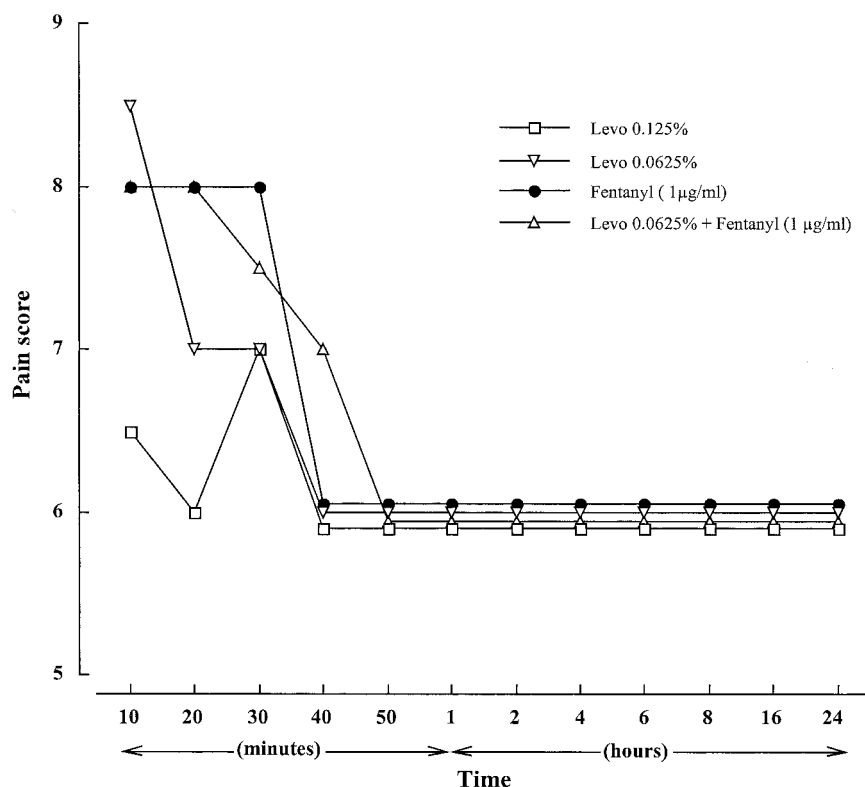


Fig. 3. Median Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) score decreased rapidly in all four groups within 60 min of the conclusion of anesthesia. The CHEOPS scores were similar for the four groups throughout the 24-h observation period. Levo = levobupivacaine.

erature nor commonly practiced. However, this practice may have augmented the effectiveness of all of the epidural blocks and in particular, the low concentration of levobupivacaine, by maintaining the level of the initial blockade with 0.175% levobupivacaine during and after surgery. Furthermore, this practice may have preserved any preemptive analgesic effects from establishing the epidural blockade before the surgical incision. Together or in part, these maneuvers may have optimized the perioperative epidural analgesia in this study.

Recognizing that levobupivacaine is effective when administered *via* the epidural route in children should reduce the risks of both acute and chronic toxicity. The

reduced risks can be attributed to several factors, including the low plasma levels of levobupivacaine after dilute concentrations (fig. 6), the reduced free levels of levobupivacaine,<sup>17</sup> and the reduced cardiotoxic and neurotoxic risk of levobupivacaine.<sup>10-12</sup>

Although fentanyl (1–3 µg/ml) is commonly combined with bupivacaine (0.1–0.25%) for perioperative epidural analgesia in children, the indication for and efficacy of epidural fentanyl in children is poorly understood. In a single-dose caudal block, 2 µg/ml plain fentanyl has been shown to provide effective analgesia in children.<sup>14</sup> As a continuous infusion, epidural fentanyl (5 µg · kg<sup>-1</sup> · day<sup>-1</sup>) has been shown to be as effective as a single dose

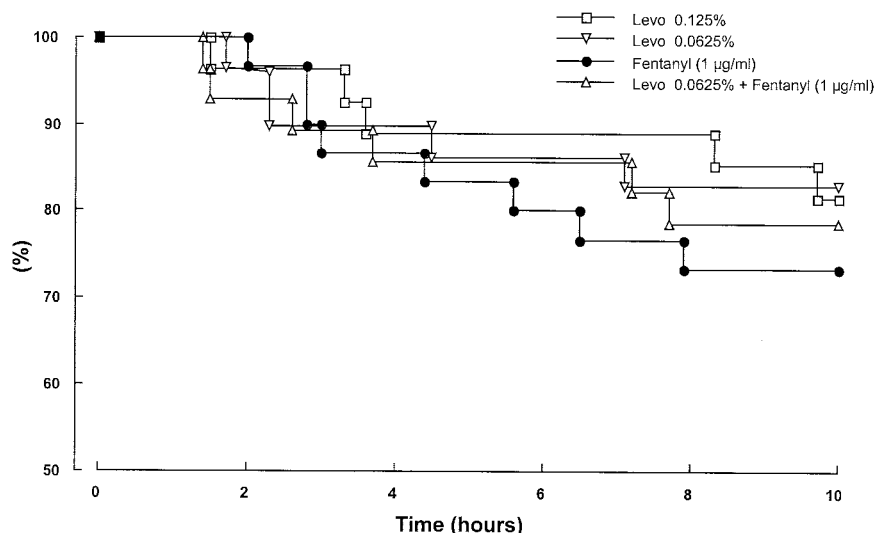


Fig. 4. Kaplan-Meier graph for children who were pain-free (*i.e.*, did not require rescue analgesics) during the first 10 h of the observation period. The numbers of children who required analgesia were similar among the four groups. Levo = levobupivacaine.

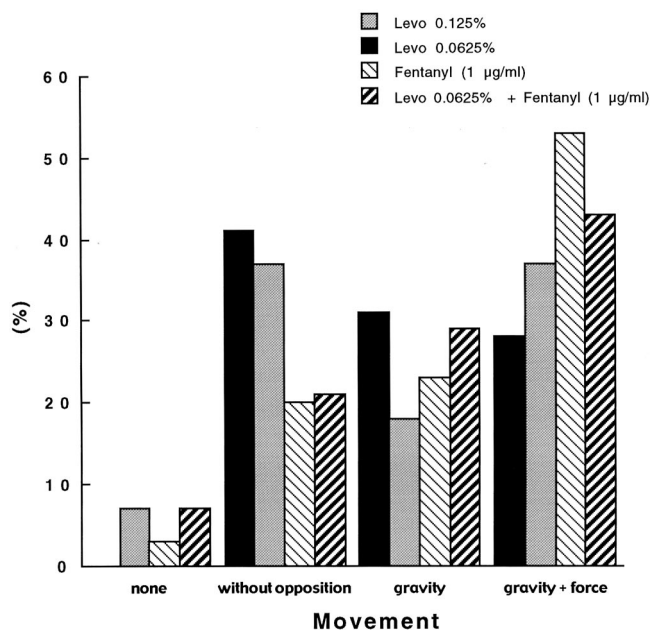


Fig. 5. Maximum motor block for the four treatments during the 24-h observation period. Maximum motor blocks were similar among the four groups. Levo = levobupivacaine. (%) indicates percentage of patients.

of epidural morphine (50 µg/kg).<sup>15</sup> However, in the latter study, the authors did not report either the mean concentration or the hourly infusion rate of epidural fentanyl. In the absence of these data, clinicians cannot use these studies to develop guidelines for the clinical practice of epidural fentanyl in children. In the current study, 1 µg/ml plain fentanyl provided near-complete analgesia for 24 h when infused at a rate of  $0.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ .

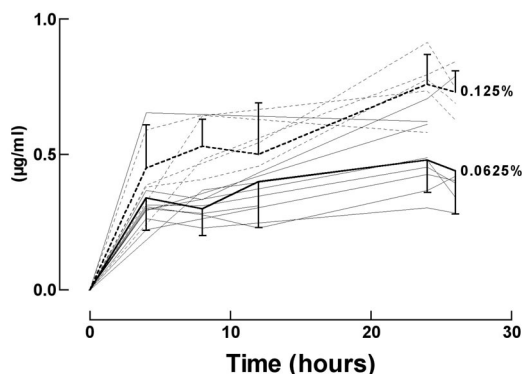


Fig. 6. Plasma concentrations of total levobupivacaine from 15 children before and during the 24 h after the start of their epidural infusions. Each *light line* represents the concentration-time profile of one child. The *heavy dashed curve* represents the mean ( $\pm$  SD) concentrations in the 0.125% levobupivacaine group, and the *heavy solid curve* represents the concentrations in the 0.0625% levobupivacaine group. The mean ( $\pm$  SD) plasma concentrations in the 0.125% levobupivacaine group ( $n = 5$ ) were approximately 50% greater than those in the 0.0625% group ( $n = 10$ ). The concentrations of levobupivacaine in both groups increased steadily during the 24 h after the start of the epidural infusions and reached maximum concentrations by 24 h. After 24 h, the epidural infusion was stopped, and the blood concentration decreased.

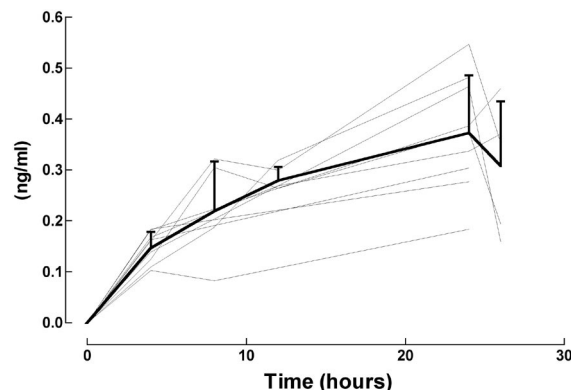


Fig. 7. Plasma concentrations of fentanyl from nine children who received epidural fentanyl with or without levobupivacaine. Each *light line* represents the concentration-time profile for one child. The *heavy line* represents the mean ( $\pm$  SD) plasma concentration-time profile for the nine children. The mean concentration of fentanyl increased steadily during the 24 h after the start of the infusions and reached a maximum concentration by 24 h.

Furthermore, the results of the current study demonstrated no benefit from combining 1 µg/ml fentanyl with even a dilute concentration of 0.0625% levobupivacaine, because the latter solution provided complete pain control.

The incidence of side effects, motor blockade, nausea, vomiting and pruritus, associated with the four epidural solutions in this study, were similar for all four treatments. In part, this may be caused by our use of dilute concentrations of analgesics, all of which confer minimal side effects. Alternately, the small sample sizes in the four treatments introduced a type II statistical error that prevented differentiation of the incidence of side effects among the four treatments. Finally, the incidence of urinary retention, a common side effect after epidural opioid use, could not be compared among the four epidural solutions because of the presence of urethral or suprapubic catheters in most of the children in this study.

The optimal concentrations of local anesthetics and opioids for epidural use are the minimal concentrations that provide effective analgesia with minimal or no side effects. Although we sought the minimal effective concentrations of the epidural medications in the current study, the analgesic effectiveness of the solutions studied precluded such a determination. Levobupivacaine, 0.0625%, was the minimal effective concentration of levobupivacaine studied, but it was also the minimal concentration studied. Until concentrations of levobupivacaine less than 0.0625% are investigated, we cannot confirm that 0.0625% levobupivacaine is the minimal effective concentration for continuous epidural analgesia in children undergoing the surgeries included in this study. Our results also suggest that the addition of 1 µg/ml fentanyl to 0.0625% levobupivacaine provides no benefit over 0.0625% plain levobupivacaine. Finally, plain fentanyl (1 µg/ml) provided slightly less effective analgesia when



administered as a continuous epidural infusion ( $0.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) than the other three solutions, but was associated with a similar side effect profile.

The authors thank Nancy Sikich, R.N. (Hospital for Sick Children, Toronto, Canada); the pain team at Bristol Royal Hospital for Sick Children (Bristol, United Kingdom); and Martine Dodman, R.N. (Royal Children's Hospital, Melbourne, Australia), for their assistance in completing this investigation.

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