Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery

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The addition of 0.125% and 0.25% bupivacaine to continuous postoperative epidural infusions of fentanyl, in a $10 \mu\text{g} \cdot \text{ml}^{-1}$ concentration, were studied in 39 patients following abdominal or thoracic surgery in prospective, random, double-blind fashion. Patients received an initial bolus of $0.1 \text{ ml} \cdot \text{kg}^{-1}$ of the study solution and an infusion of $6 \text{ ml} \cdot \text{hr}^{-1}$ which was titrated to maintain analgesia ($\text{VAS} < 40$). Assessments of pain (VAS), pulmonary function (pH, PaCO_2), and bowel function (time to flatus or po fluids) were made until the second postoperative morning. There was a difference among the three groups in analgesia (means VAS scores) over time ($P < 0.01$), with the fentanyl-alone group producing less analgesia than the 0.125% bupivacaine group ($P < 0.01$). There was no difference in the average infusion rates, postoperative pulmonary function, or bowel function. The incidence of side effects including somnolence, nausea and vomiting, and pruritus was also similar.

Key words

ANAESTHETIC TECHNIQUES: epidural;
PAIN: postoperative;
ANALGESICS: fentanyl;
ANAESTHETICS, LOCAL: bupivacaine.

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Fewer patients in the 0.125% bupivacaine group than in the 0.25% group developed a transient sensory loss to pinprick and ice (3 vs 10, $P < 0.001$). Four patients in both bupivacaine groups had leg weakness, those in the 0.125% were all a Bromage 1 score, while in the 0.25% group one had a Bromage 1, one a Bromage 2, and two Bromage 3 scores. The addition of 0.125% bupivacaine improves the analgesia of epidural infusions of fentanyl ($10 \mu\text{g} \cdot \text{ml}^{-1}$) when used following abdominal or thoracic surgery and results in minimal sensorimotor disturbance.

L'ajout de bupivacaine 0,125% et 0,25% à une perfusion épidurale continue de fentanyl $10 \mu\text{g} \cdot \text{ml}^{-1}$ est étudié prospectivement, après répartition au hasard et à double aveugle chez 39 patients après une chirurgie viscérale ou thoracique. Les patients reçoivent un bolus de $0,1 \text{ ml} \cdot \text{kg}^{-1}$ de la solution à l'étude et une perfusion de $6 \text{ ml} \cdot \text{hr}^{-1}$ titrée de façon à maintenir l'analgesie ($\text{EVA} < 40$). La douleur (EVA), les fonctions respiratoires (pH, PaCO_2) et digestives (reprise du transit intestinal ou liquides po) sont évaluées jusqu'au matin du deuxième jour postopératoire. L'étude révèle une différence entre les trois groupes pour l'analgesie (scores moyens sur l'EVA) en fonction du temps ($P < 0,01$): l'analgesie produite chez le groupe fentanyl-seul est inférieure à celle du groupe bupivacaine 0,125% ($P < 0,01$). La vitesse de perfusion, les fonction respiratoires et intestinales ne diffèrent pas. L'incidence des effets secondaires, dont la somnolence, les nausées et vomissements, et le prurit est identique. Moins de patients du groupe bupivacaine 0,125% que du groupe bupivacaine 0,25% développent une perte de sensibilité à la piqure et à la glace (3 vs 10, $P < 0,001$). Quatre patients parmi chaque groupe bupivacaine présentent de la faiblesse aux membres inférieurs; ceux du groupe bupivacaine 0,125% sont tous cotés Bromage 1, alors que dans le groupe bupivacaine 0,25, un est coté Bromage 1, un Bromage 2, et deux Bromage 3. L'ajout de bupivacaine 0,125% améliore l'analgesie produite par les perfusions épidurales de fentanyl ($10 \mu\text{g} \cdot \text{ml}^{-1}$) en chirurgie viscérale et thoracique et provoque peu de perturbations sensitives et motrices.

Recently, some authors have recommended that epidural infusions used for the treatment of postoperative pain contain a narcotic combined with a local anaesthetic.^{1,2} Theoretically, since the two drugs act by different mechanisms their effects should be additive, thus leading to decreased requirements for each drug and thereby minimizing their individual side effects. Side effects from epidural local anaesthetics include sympathetic blockade leading to postdural hypotension, as well as sensory and/or motor blockade yielding difficulty with ambulation. Respiratory depression, pruritus, nausea and vomiting, and urinary retention are side effects attributable to epidural narcotics.

However, effective local anaesthetic-narcotic combinations that minimize side effects have not been determined. The addition of bupivacaine 0.1% did not improve analgesia with epidural morphine following either thoracotomy³ or upper abdominal surgery,⁴ nor did it improve epidural fentanyl analgesia in patients having undergone either orthopaedic,⁵ or abdominal and thoracic surgery.⁶ The addition of higher bupivacaine concentrations of 0.2–0.25% to both epidural morphine and fentanyl has improved postoperative analgesia following abdominal surgery,⁷ aortic surgery,⁸ and thoracic surgery.⁹ However, in these studies there was a high incidence of sensory blockade (30–100% of patients), which is not optimal for early ambulation. A more effective concentration may therefore lie between these extremes, such as bupivacaine 0.125%. This concentration, when added to epidural sufentanil, produced superior analgesia to post-thoracotomy patients when compared with sufentanil alone. In this study though, no measurement of sensory and motor function was made.¹⁰

The purpose of the present study was, therefore, to determine if bupivacaine 0.125% added to continuous epidural fentanyl infusions either produced superior analgesia or reduced fentanyl requirements while minimizing side effects in comparison with both fentanyl alone, and with a fentanyl–0.25% bupivacaine combination given in random, double-blind fashion to patients undergoing abdominal or thoracic surgery.

Methods

Following institutional approval and written informed consent, ASA physical status I–III patients undergoing elective abdominal or thoracic surgery who had agreed to receive postoperative epidural analgesia were considered for study. Exclusion criteria included patients >75 yr of age, weight >100 kg, or those with pre-existing neurological deficit, and/or psychiatric history.

Preoperatively, patients had an epidural catheter in-

serted by the attending anaesthetist. The injection of 3 ml, CO₂ lidocaine 2% was used to exclude subarachnoid placement. Patients received general anaesthesia for their procedures. Intraoperatively, the epidural catheter was used for anaesthesia at the discretion of the attending anaesthetist. At the beginning of wound closure, patients received an epidural bolus of 0.1 ml · kg⁻¹ of the study solution followed by a continuous infusion of 6.0 ml · hr⁻¹ using a syringe pump (Model 710, Ivac Corp.) If at any time the pain score was >40 (see below), an epidural bolus dose of 3.0 ml of the study solution was given and the infusion rate was increased by 2.0 ml · hr⁻¹. If at any time after leaving the recovery room the patient was drowsy and/or somnolent (somnolence score >3, see below), the infusion rate was decreased by 2.0 ml · hr⁻¹. The infusion syringes were prepared in a randomized, double-blind fashion by the hospital pharmacy. Randomization was determined with the use of a random number table. The three solutions consisted of fentanyl in a concentration of 10 µg · ml⁻¹ alone (fentanyl), fentanyl with the addition of bupivacaine 0.125% (fent-0.125%), or fentanyl with bupivacaine 0.25% (fent-0.25%). All solutions were prepared by dilution with preservative-free normal saline.

Postoperatively, patients remained in the post-anaesthesia care unit (PACU) for two to three hours and then were transferred to the ward where respiratory rate and somnolence were monitored hourly, while blood pressure and heart rate were recorded every four hours. Supplemental oxygen therapy was initiated in the recovery room at the discretion of the attending anaesthetist and/or surgeon.

Analgesia was assessed using a visual analogue scale (VAS; 0 = no pain and 100 = worst pain ever). Side effects were measured using the following scales: somnolence (1 = oriented and initiates conversations, 2 = responds to all forms of stimulation but does not talk, 3 = disoriented, but responds to commands and pain, 4 = responds to pain only, 5 = unresponsive), nausea, vomiting, and pruritus (0 = none, 1 = mild and no treatment required, 2 = moderate, treatment effective, 3 = severe, treatment not effective). Sensory loss was determined by response to pinprick and ice, motor blockade was quantified using a modified Bromage scale,¹¹ and the presence of postural hypotension was recorded if blood pressure decreased >30/20 mmHg upon sitting.¹² These measurements were made prior to discharge from the PACU (PACU D/C), on the morning and afternoon of the first postoperative day (POD1AM, POD1PM), and on the morning of the second postoperative day (POD2AM) by a trained research nurse. Blood gas analysis was performed at PACU D/C, POD1AM and

TABLE I Demographic data. Values are mean $\pm$ SD with the exception of epidural location which are median, and ranges below

	Fentanyl	Fent-0.125%	Fent-0.25%
<i>n</i>	14	13	12
Age (yr)	61 $\pm$ 10	62 $\pm$ 9	59 $\pm$ 12
Height (cm)	172 $\pm$ 7	167 $\pm$ 5	168 $\pm$ 10
Weight (kg)	80 $\pm$ 4	76 $\pm$ 12	66 $\pm$ 15*
Sex (m:f)	11:3	12:1	8:4
Epidural (median)	T ₁₁₋₁₂	L ₁₋₂	L ₁₋₂
(range)	T ₇₋₈ -L ₃₋₄	T ₇₋₈ -L ₃₋₄	T ₇₋₈ -L ₃₋₄
Procedure			
- Urological	3	5	5
- General surgical	3	2	4
- Thoracic	8	6	3
Intraoperative blockade			
- Yes/no	5/9	5/8	6/6
- Bupivacaine (mg)	12 $\pm$ 29	22 $\pm$ 24	23 $\pm$ 34
Intraoperative narcotics			
- Fentanyl equivalents (μ g)	500 $\pm$ 230	460 $\pm$ 320	365 $\pm$ 130

* $P < 0.05$.

POD2AM. The times after surgery until first flatus and first *po* fluids were also documented.

Demographic comparisons were made using unpaired Student's *t* tests for parametric data and chi-square analysis for nonparametric data. Pain scores, infusion rates, blood gas and oxygen saturation results were compared using analysis of variance for repeated measures with Fisher's protected least significant difference test to determine between group differences. Side effects were compared with Kruskal-Wallis analysis of variance. A *P* value < 0.05 was considered significant.

Results

Thirty-nine ASA physical status I-III patients undergoing elective abdominal or thoracic surgery were studied. Demographic data are summarized in Table I. There were no differences in the age, height, sex distribution or location of the epidural catheter among the three groups with the exception that patients in the bupivacaine 0.25% group weighed less. Surgical procedures were defined as major urological (total cystectomies, radical prostatectomies, nephrectomies, adrenalectomies), general surgical (abdomino-perineal resections, anterior resections, Whipple's procedures, and hepatic lobectomies), and thoracotomies. There was no difference in the distribution of these procedures among the three groups. There were no differences in the amounts of intraoperative opioids that patients received among the three groups expressed as fentanyl equivalents (1 μ g sufentanil = 10 μ g fentanyl). There was also no difference in the number of patients receiving

FIGURE 1 Analgesia as measured using visual analogue scale (VAS) pain scoring. Values are mean $\pm$ SEM. * $P < 0.01$ fent vs fent-0.125%.

intraoperative epidural local anaesthesia either in number or dosage among the groups.

The average pain scores at the different measurement times are shown in Figure 1. The mean pain VAS scores ranged between 10–50 mm during the study period. There was a difference in the VAS scores among the three groups over the study period, $P < 0.01$. The plain fentanyl group had higher VAS scores than the bupivacaine 0.125% group ($P < 0.01$), but greater than the bupivacaine 0.25% group ($P = 0.07$). During the study the infusion rates averaged 5–8 $\text{ml} \cdot \text{hr}^{-1}$, with the bupivacaine groups patients' tending to require lower infusion rates; however, this difference was not statistically significant (Figure 2). The times to first flatus and to first *po* fluids

FIGURE 2 Epidural infusion rates during the study in $\text{ml} \cdot \text{hr}^{-1}$. Values are mean $\pm$ SEM. NS differences.

TABLE II Time to return of bowel function. Values are mean $\pm$ SEM. NS differences

	Fentanyl	Fent-0.125%	Fent-0.25%
Flatus time (days)	3.2 $\pm$ 0.6	4.2 $\pm$ 0.4	3.5 $\pm$ 0.7
po fluids (days)	2.7 $\pm$ 0.6	3.7 $\pm$ 0.9	4.2 $\pm$ 1.0

are shown in Table II. There were no differences in either of these variables among the three groups.

The mean pH ranged from 7.35–7.41 and the mean PaCO_2 from 40–45 mmHg during the study period. There were no differences in these measurements among the three groups. There was no difference in the number of patients receiving supplemental oxygen or the inspired oxygen concentration administered to patients between the three groups.

The severity of side effects including nausea and vomiting, pruritus, and somnolence are listed in Table III. There were no instances of postural hypotension. The incidence of these side effects was no different at any of the measurement times among the three groups. Three patients in the bupivacaine 0.125% group as opposed to ten patients in the bupivacaine 0.25% group developed sensory losses to both ice and pinprick ($P < 0.001$). Also, four patients in the 0.125% group experienced a motor weakness of Bromage scale 1, while in the 0.25% group four patients had varying motor weakness (one Bromage 1, one Bromage 2, and two Bromage 3 score).

Discussion

This study demonstrates that the addition of bupivacaine 0.125% to epidural fentanyl in a $10 \mu\text{g} \cdot \text{ml}^{-1}$ concentration given as a continuous infusion improves analgesia following abdominal and thoracic surgery. This is in con-

trast to the 0.1% concentration, which did not improve analgesia either when added to epidural morphine following thoracotomy,³ or upper abdominal surgery,⁴ or to epidural fentanyl following knee joint replacement,⁵ or abdominal and thoracic surgery.⁶ This likely represents the effect of the additional bupivacaine, approximately $1.75 \text{ mg} \cdot \text{hr}^{-1}$ ($[0.125\% - 0.1\%] \times 7 \text{ ml} \cdot \text{hr}^{-1}$), since the patients' pain scores in the fentanyl group were similar to patients' pain scores in studies using either epidural infusions of fentanyl combined with 0.1% bupivacaine,^{5,6,13} or those using epidural fentanyl alone involving similar procedures.^{14–16} This finding is consistent with other studies where the use of bupivacaine 0.125% has provided improved postoperative analgesia when mixed with continuous infusions of epidural sufentanil following thoracotomy,¹⁰ and when combined with a continuous infusion of diamorphine following lower abdominal surgery.¹⁷ Recently, this concentration of bupivacaine has been shown to decrease opioid requirements when used with fentanyl $5 \mu\text{g} \cdot \text{ml}^{-1}$ and delivered by patient-controlled bolus epidural after orthopaedic surgery.¹⁸

The bupivacaine 0.25% group pain scores were not lower than in the plain fentanyl group. This was most likely the result of the titration protocol that was used. This led to the situation where both the pain scores and infusion rates were lower but not different from the plain fentanyl group. This explanation is supported by previous studies where the addition of bupivacaine 0.25% to epidural morphine showed improved postoperative epidural analgesia following abdominal surgery,⁷ and the use of 0.2% bupivacaine has enhanced continuous epidural fentanyl pain relief following both abdominal aortic surgery,⁸ and thoracic surgery.⁹

There were no differences in the secondary respiratory and alimentary outcome variables which included PaCO_2 , pH, and times to flatus and po fluids. This is similar to other studies using concentrations of bupivacaine varying from 0.1–0.5% with either fentanyl or morphine.^{4,6,9,10,19–22} The majority of our patients did not experience opioid-related side effects, which is similar to results reported by others using epidural fentanyl with and without bupivacaine.^{5,6,8,9,13–16} The incidence of bupivacaine-related side effects of sensory loss was less with 0.125% (3/13) than in the 0.25% group (10/12). For the 0.125% group this compares favourably with other studies using bupivacaine 0.2–0.5% where sensory loss has varied from 30–100% of patients.^{2,7–9,20–22} Previous studies using bupivacaine 0.125%, either did not measure sensory function,¹⁰ measured it in conjunction with an initial block using bupivacaine 0.5%,¹⁸ or used infusion rates of $15 \text{ ml} \cdot \text{hr}^{-1}$,¹⁷ making comparisons difficult. Though the incidence of motor blockade was similar with both bupivacaine concentrations, the degree of

TABLE III Side effects experienced at the measurement times using scoring system defined in the text. Values are medians with ranges. NS differences

Group	Pruritus	Nausea and vomiting	Somnolence
PACU D/C Fentanyl	0 (0-1)	0 (0-3)	1 (1-3)
Fent-0.125%	0 (0-1)	0 (0-1)	1 (1-3)
Fent-0.25%	0 (0-1)	0 (0-1)	1 (1-2)
PODIAM Fentanyl	0 (0-2)	0 (0-2)	1 (1-2)
Fent-0.125%	0 (0-2)	0 (0-1)	1 (1-2)
Fent-0.25%	0 (0-1)	0 (0-2)	1 (1-2)
PODI PM Fentanyl	0 (0-2)	0 (0-2)	1
Fent-0.125%	0 (0-2)	0 (0-2)	1
Fent-0.25%	0 (0-2)	0 (0-2)	1 (1-3)
POD2AM Fentanyl	0 (0-1)	0 (0-1)	1 (1-3)
Fent-0.125%	0 (0-1)	0 (0-2)	1 (1-2)
Fent-0.25%	0 (0-2)	0	1

blockade was more pronounced with the 0.25% concentration as higher Bromage scores resulted. Reported incidences of motor blockade with bupivacaine 0.2–0.25% were similar to ours,^{2,7–9} while those studies using 0.5% did not measure motor function.^{20–22}

Our protocol did not include establishing a defined sensory block prior to or during surgery. We also did not standardize the intraoperative opioid usage. However, there were no differences intraoperatively among the three groups in the amount of narcotic used nor in the amount of epidural local anaesthetic received. Therefore, we feel that neither variable affected our results.

In this study we measured VAS pain scores with patients at rest as has been done in many postoperative epidural opioid studies.^{3–6,8,9,13–17,19–22} Dahl *et al.*'s work comparing morphine with and without bupivacaine 0.25%⁷ showed that differences in analgesia were undetectable at rest but were evident with coughing or exercise. In spite of this, we were able to show the beneficial effect of adding bupivacaine 0.125% in terms of decreasing analgesia at rest.

In summary, we have shown that in patients having abdominal or thoracic surgery, the addition of bupivacaine 0.125% to epidural infusions of fentanyl provides improved analgesia over using fentanyl alone. There were no differences in other outcome variables including pulmonary or bowel function, while 3/13 patients had sensory changes and 4/13 had minor motor weakness.

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