Bupivacaine 0.1% does not improve post-operative epidural fentanyl analgesia after abdominal or thoracic surgery

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Epidural infusions of fentanyl, in a 10 $\mu g \cdot ml^{-1}$ concentration, combined with bupivacaine 0.1% were compared with epidural infusions of fentanyl alone for postoperative analgesia following abdominal or thoracic surgery. There were no detectable differences between the two groups in analgesia (mean visual analogue scale pain scores ranging between 15–35 mm), average infusion rates of 7–9 $ml \cdot hr^{-1}$, and serum fentanyl concentrations which reached 1–2 $ng \cdot ml^{-1}$. There was no difference in postoperative pulmonary function (pH, $PaCO_2$, SaO_2), or bowel function (time to flatus or po fluids). The incidence of side-effects including somnolence, nausea and vomiting, pruritus and postural hypotension was also similar. Of the patients receiving fentanyl and bupivacaine 0.1%, three developed a transient unilateral sensory loss to pinprick and ice, and two of these patients had unilateral leg weakness equal to a Bromage 1 score. The addition of bupivacaine 0.1% does not improve epidural infusions of fentanyl using a 10 $\mu g \cdot ml^{-1}$ concentration following abdominal or thoracic surgery.

L'administration épidurale de fentanyl à la concentration de 10 $\mu g \cdot ml^{-1}$, associée à de la bupivacaïne 0,1%, a été comparée à une perfusion épidurale de fentanyl dans le traitement de la douleur suite à une chirurgie abdominale ou thoracique. Aucune différence significative n'a été observée entre les groupes pour la qualité de l'analgésie (la moyenne du pointage à l'échelle de la douleur visuelle analogue variant entre 15 et 35 mm), avec des perfusions moyennes de 7 à 9 $ml \cdot h^{-1}$, et des concentrations sériques de fentanyl de 1 à 2 $ng \cdot ml^{-1}$. Il n'y a pas eu de différence dans la fonction pulmonaire postopératoire (pH, $PaCO_2$, SaO_2), ni dans le temps de reprise du transit digestif (flatulence et hydratation orale). L'incidence d'effets secondaires tels la somnolence, les nausées et vomissements, le prurit et l'hypotension orthostatique était comparable entre les groupes. Trois patients traités avec le mélange fentanyl et bupivacaïne 0,1% ont présenté une hypoesthésie transitoire et unilatérale (au froid et à la piqûre), et deux d'entre eux ont eu une parésie d'une jambe, équivalente à 1 sur l'échelle de Bromage. L'addition de bupivacaïne 0,1% au fentanyl (10 $\mu g \cdot ml^{-1}$) donné en perfusion épidurale n'améliore pas la qualité de l'analgésie après une chirurgie abdominale ou thoracique.

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

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A recent advance in the treatment of postoperative pain has been the use of epidural infusions of narcotic combined with a local anaesthetic, usually bupivacaine. 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 postural hypotension, as well as sensory and/or motor blockade yielding difficulty with ambulation. Respiratory depression, pruritus, urinary retention, as well as nausea and vomiting are side-effects due to epidural narcotics.

Though this technique has become popular, the optimum effective combination has not been determined. Despite this, the use of bupivacaine in 0.1% concentration is common. However, when combined with morphine this combination was no better than an infusion of epidural

morphine alone in terms of analgesia, total narcotic requirements, and the incidence of nausea or pruritus following either thoracotomy[1] or upper abdominal surgery.[2] Attention has turned to epidural infusions of fentanyl because of its lower incidence of pruritus, nausea and vomiting,[3–5] and the fact that it may not cause clinically important respiratory depression.[4–7] When fentanyl in a 10 $\mu g \cdot ml^{-1}$ concentration was combined with bupivacaine 0.1% as an epidural infusion it was effective for postoperative pain management,[8–11] although the dosages of fentanyl used in these studies may have been sufficient to supply analgesia alone.[6,7,12] The only double-blind, randomized study comparing an infusion of this combination of epidural fentanyl and bupivacaine 0.1% with an infusion of epidural fentanyl alone, was found to be no more effective in terms of improved analgesia or decreased side-effects in patients having undergone elective total knee joint replacement.[13] This may have been because bupivacaine 0.1% was insufficient for the somatic pain that these orthopaedic patients experienced. Since visceral pain is transmitted through the sympathetic nervous system, which has a higher proportion of smaller, unmyelinated nerve fibres,[14] it may be more susceptible to the beneficial effects of the low concentration of 0.1% bupivacaine. Therefore, this study compared in random, double-blind fashion the effects of epidural infusions of fentanyl in a 10 $\mu g \cdot ml^{-1}$ concentration and bupivacaine 0.1% with fentanyl alone in patients experiencing visceral pain after 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. Patients greater than 75 yr of age, weight greater than 100 kg, or those with pre-existing neurological deficit, and/or psychiatric history, were excluded from the study.

Preoperatively, patients had an epidural catheter inserted by the attending anaesthetist. Its position was verified with the use of lidocaine 2% CO_2. Intraoperatively, patients received a combined general and epidural anaesthetic at the discretion of the attending anaesthetist, and were monitored in the routine fashion. Upon initiation of wound closure, patients received an epidural bolus of 0.1 $ml \cdot kg^{-1}$ of the study solution followed by a continuous infusion of 6.0 $ml \cdot hr^{-1}$ using a standardized syringe pump as in our previous study.[13] If at any time the pain score was >33 (see below), an epidural bolus dose of 3.0 ml of the study solution was given and the infusion was increased by 2.0 $ml \cdot hr^{-1}$. If at any time following recovery room departure the patient was drowsy and/or somnolent (somnolence score >3, see below), the infusion rate was decreased by 2.0 $ml \cdot hr^{-1}$. The infusion syringes were prepared in randomized, double-blind fashion by the hospital pharmacy through the use of a random number table. The solutions used were fentanyl in a concentration of 10 $\mu g \cdot ml^{-1}$ with or without the addition of bupivacaine 0.1% (1 $mg \cdot ml^{-1}$) diluted with preservative-free normal saline.

Postoperatively, patients remained in the recovery room 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. Oxygen saturation was measured continuously using an 8800 Cardiorespiratory Oximeter (Nonin Medical Inc., Associated Respiratory Services, Mississauga, Ont.) which supplied a hard copy and summary information when in playback mode.

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 as treatment effective, 3 = severe, as treatment not effective). Sensory loss was determined by response to pinprick and ice, motor blockade was quantified using a modified Bromage scale,[15] and the presence of postural hypotension was recorded if blood pressure decreased >30/20 mm Hg upon sitting.[16] These measurements were made prior to recovery room departure (RRD), 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 for blood gas analysis was sampled at RRD, POD1AM and POD2AM. Venous samples for analysis of serum fentanyl concentration were also taken at the final assessment. Samples were centrifuged and stored at −20° C until fentanyl analysis was performed using a commercial radioimmunoassay kit[7] (Janssen Laboratories, Beerse, Netherlands). This assay is sensitive to 0.1 $ng \cdot ml^{-1}$ with intra-assay and inter-assay coefficients of variation of 6.0% and 7.0%, respectively at 1.0 $ng \cdot ml^{-1}$. 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 two-factor ANOVA for repeated measures. Side-effects were compared with Mann-Whitney U analysis.

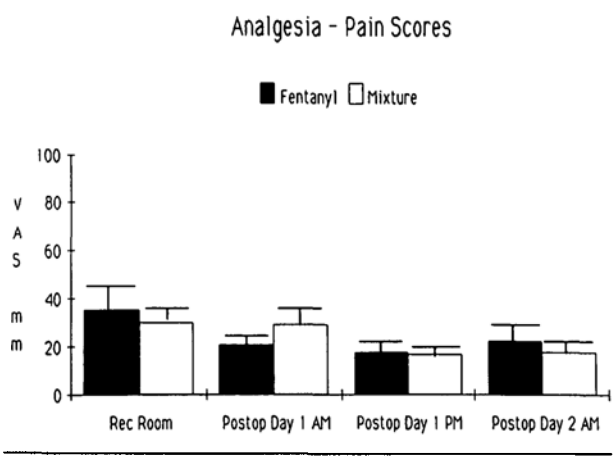

FIGURE 1 Analgesia measured using visual analogue scale (VAS) pain scoring. Values are mean ± SEM. NS.

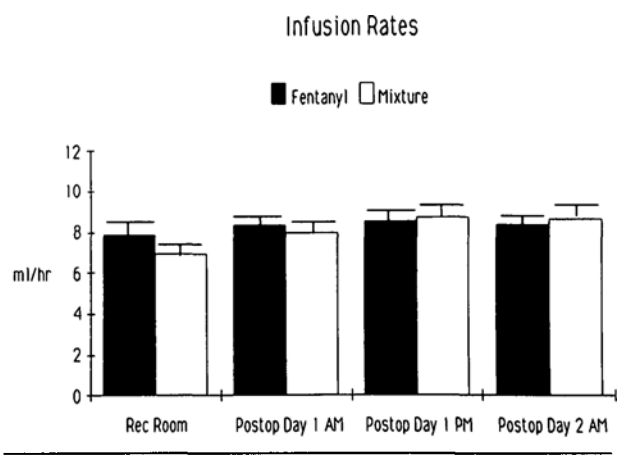

FIGURE 2 Epidural infusion rates during the study in ml/hr. Values are mean ± SEM. NS.

TABLE I Demographic data

	Fentanyl	*Mixture*
n	15	15
Age (yr)	53 ± 16	57 ± 14
Height (cm)	165 ± 18	170 ± 11
Weight (kg)	83 ± 30	79 ± 12
Sex (m:f)	11:4	11:4
Epidural (median)	L_{2-3}	L_{1-2}
(range)	$T_{11-12} - L_{4-5}$	$T_{11-12} - L_{4-5}$
Procedure		
– Major urologic	2	6
– Retroperitoneal	7	5
– Major general	7	5
– Thoracic	3	2

Demographic data. Values are mean ± SD with the exception of epidural location which are median, and ranges below. NS differences.

Results

Thirty ASA physical status I–III patients undergoing elective abdominal or thoracic surgery were studied. Their demographic data are summarized in Table I. There were no differences in the age, weight, height, sex distribution or location of the epidural catheter between the two groups. Surgical procedures were defined as major urologic (total cystectomies, and radical prostatectomies), retroperitoneal (nephrectomies, adrenalectomies), major general (abdomino-perineal resections, anterior resections, Whipple's procedures, and hepatic lobectomies), and thoracotomies. There was no difference in the distribution of these procedures between the two groups. Four patients, two from each group, were removed from the study after the POD1PM measurement due to catheter dislodgement which was diagnosed by physical examination and/or testing with lidocaine 2% CO_2.

The average pain scores at the different measurement times are shown in Figure 1. The mean pain scores ranged between 15–35 mm during the study period. There were no differences between either group at any of the measurement times. The average infusion rates in each group are shown in Figure 2. After recovery room departure the infusion rates averaged 7–9 $ml \cdot hr^{-1}$ over the next 48 hr. Again, there were no statistically or clinically significant differences in mean infusion rates between patients receiving epidural fentanyl and those receiving epidural fentanyl and bupivacaine.

The time to first flatus was 3.0 ± 0.5 days for the fentanyl patients and 3.5 ± 0.5 days for the mixture patients, and the time to first *po* fluids was 3.4 ± 0.8 days for the fentanyl group and 3.8 ± 0.6 days for the mixture group (mean ± SEM, NS). At the study completion, the average serum fentanyl concentrations were 1.75 ± 0.28 $ng \cdot ml^{-1}$ for the epidural fentanyl patients and 2.39 ± 0.26 $ng \cdot ml^{-1}$ for the fentanyl and bupivacaine group (mean ± SEM, NS).

The mean pH and $PaCO_2$ values at the three measurement times are shown in Figures 3 and 4. The mean pH ranged from 7.36–7.39 and $PaCO_2$ from 38–45 mmHg. Although there appears to be a difference prior to recovery room departure, this was not statistically significant as were the other measurements. There was no difference between the two groups in the percentage of time desaturated for any of these intervals (Table II). There was no difference in the number of patients receiving supplemental oxygen or the concentration administered between the two groups. During the first postoperative day patients had $SpO_2 < 90\%$ for up to 18% of the time; however, this included times when patients were not receiving their oxygen when eating, washing, etc. but there was no difference between the two groups. Three patients experienced $SpO_2 < 80\%$; one was receiving the mixture, and

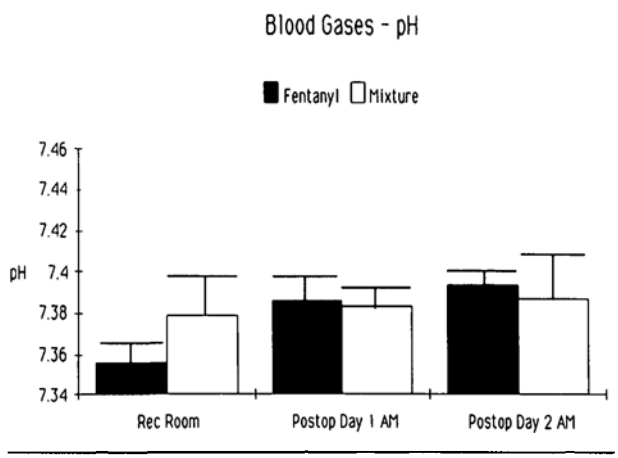

FIGURE 3 Blood gas pH values at the times shown. Values are mean ± SEM. NS.

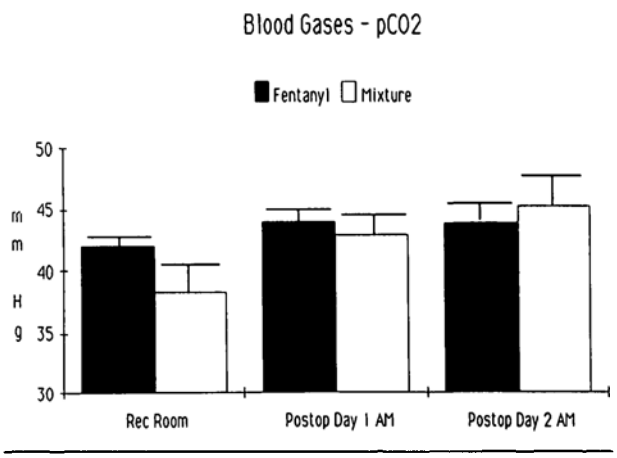

FIGURE 4 Blood gas $PaCO_2$ values in mmHg at the times shown. Values are mean ± SEM. NS.

TABLE II Oxygen saturation <90%

	Fentanyl	*Mixture*
RRD – POD1AM	5.6 ± 2.8	6.2 ± 2.5
POD1AM – POD1PM	17.9 ± 7.1	13.3 ± 6.3
POD1PM – POD2AM	14.2 ± 6.2	8.2 ± 4.1

Oxygen saturation < 90% expressed as the percentage of time monitored. Values are mean ± SEM. NS.

two were receiving epidural fentanyl alone. Of these patients, one had undergone a thoracotomy and developed a persistent collapse of his remaining lung, the second had bilateral atelectasis, and the third had severe chronic obstructive lung disease preoperatively yet received no supplemental oxygen after surgery.

The severity of side-effects including somnolence, nausea and vomiting, pruritus, and postural hypotension are listed in Table III. There were no differences in the incidences of any of these side-effects at any of the measurement times between the groups. Three patients in the fentanyl and bupivacaine group developed unilateral sensory losses to both ice and pinprick and two of these experienced a motor loss (Bromage scale = 1) which resolved upon discontinuation of the epidural infusion and did not affect their postoperative course. One patient who had been in the epidural fentanyl group died after POD2AM; however, a hospital review decided that this was unrelated to the epidural narcotic.

Discussion

Although there have been several reports of the use of epidural infusions of fentanyl in a 10 $\mu g \cdot ml^{-1}$ concentration combined with bupivacaine 0.1%,[9–11] none has been double-blind or randomized. As the amount of fentanyl used with bupivacaine in these studies was similar to that used in studies using infusions of epidural fentanyl alone,[6,7,12] we felt that double-blind, randomized studies confirming this practice were necessary. Our initial study showed that 0.1% bupivacaine did not improve epidural fentanyl analgesia following total knee joint replacement using the same 10 $\mu g \cdot ml^{-1}$ fentanyl concentration.[13] However, since the knee is innervated by somatic nerves, which are relatively large and myelenated,[14] we considered that the 0.1% concentration of bupivacaine may still have been effective for visceral pain, with its smaller, sympathetically mediated innervation, and hence felt the study should be repeated in postoperative abdominal and thoracic surgery patients.

We were able to obtain pain scores in our postoperative abdominal or thoracic patients similar to those acquired in our previous study,[13] as well as in those studies using epidural infusions of fentanyl combined with 0.1% bupivacaine,[9–11] or those using fentanyl alone.[6,7,12] Also, the infusion rates that our patients required were similar to those used in these other studies while using identical fentanyl and/or bupivacaine concentrations. We believe that a clinically important difference in the VAS of 20 mm or of 2 $ml \cdot hr^{-1}$ in infusion rates would be necessary to warrant using the fentanyl-bupivacaine combination. Using these values and the Altman nomogram[18] the power of this study is 0.78 and therefore sufficient to support our conclusions. There were no differences in the secondary outcome variables which included respiratory function ($PaCO_2$, pH, SaO_2) as well as bowel function (time to flatus and *po* fluids). The majority of our patients did not experience side-effects, which is similar to reports by others using the fentanyl and bupivacaine combination.[9–11] Thus, we are confident that the addition of 0.1% bupivacaine does not improve postoperative analgesia nor

TABLE III Side-effects

	Fentanyl			*Mixture*		
	Pruritus	*Nausea and vomiting*	*Somnolence*	*Pruritus*	*Nausea and vomiting*	*Somnolence*
Rec Rm	0(0–1)	0(0–2)	1(1–2)	0(0–1)	0(0–3)	1(1–3)
POD1AM	0(0–1)	0(0–2)	1(1–2)	0(0–1)	0(0–2)	1(1–2)
POD1PM	0(0–1)	0(0–3)	1(1–2)	0(0–1)	0(0–2)	1(1–2)
POD2AM	0(0–2)	0(0–3)	1(1–2)	0(0–1)	0(0–2)	1(1–2)

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

decrease the incidence of side-effects in abdominal or thoracic patients.

The addition of 0.1% bupivacaine to epidural fentanyl does not appear to inhibit fentanyl uptake from the epidural space into the spinal cord, as the mean plasma fentanyl levels in both groups were not different when measured at the study completion. These findings are consistent with other studies using epidural fentanyl infusions.[6,7,13,19]

The 0.1% concentration of epidural bupivacaine is probably insufficient to offer an advantage even in patients with postoperative visceral pain. Scott *et al.*,[20] and Hjortso *et al.*[21] when using epidural infusions of 0.5% bupivacaine alone for postoperative analgesia following upper abdominal surgery needed rates similar to ours of 6–8 ml · hr^{-1}. In these patients, the addition of morphine improved analgesia though not respiratory or endocrine function. Conversely, in an unblinded study, Bisgaard *et al.*, using a 0.25% bupivacaine plus 0.06 mg · ml^{-1} morphine solution, provided superior analgesia to epidural morphine alone in abdominal surgery patients.[22] The majority of patients receiving only the 0.5% bupivacaine infusion had sensory losses,[19,20] which is presumably why many investigators using a narcotic-bupivacaine combination have chosen the lower dosage of 0.1%. However, most double-blind studies using low bupivacaine concentrations have found no benefit. Continuous epidural infusions of hydromorphone and 0.08% bupivacaine have been shown recently to be no more beneficial than hydromorphone alone for pain after Caesarean section.[23] Similarily, when morphine alone was compared with morphine and 0.1% bupivacaine as epidural infusions in patients after thoracotomy,[1] or after abdominal surgery,[2] no difference in analgesia or side-effects was found, though both were superior to systemic narcotics or epidural bupivacaine alone. The only double-blind study claiming beneficial effects of adding low-dose (0.125%) bupivacaine to an epidural narcotic infusion, in this case diamorphine following hysterectomy, used infusion rates of 15 ml · hr^{-1}.[24] However, all patients developed motor and sensory deficits and, in fact, all patients required supplemental analgesia. These results combined with the fact that in animal models spinal narcotics and local anaesthetics have been shown to be synergistic,[25] suggests that a higher concentration of bupivacaine with epidural fentanyl or any other narcotic, is needed for optimum postoperative pain relief.

These findings in postoperative patients are different from those reported in obstetrical patients where infusions of fentanyl, [26–27] sufentanil,[27,28] and alfentanil[27] mixed with 0.125% bupivacaine have supplied analgesia superior to that provided by infusions of bupivacaine alone. This may simply be because the extra 0.25 mg · ml^{-1} of bupivacaine infused at 7–10 ml · hr^{-1} (1.75–2.5 mg · hr^{-1}) to the obstetrical patients was enough to supply the added analgesia necessary to show a difference when compared to our patients. A second reason may be that labour pain is different from postoperative pain as it is not relieved by narcotics alone.[29] Lastly, the different results may be because comparisons have been made only with plain bupivacaine rather than fentanyl alone as we have done. As noted earlier a mixture of 0.1% bupivacaine and morphine has been shown to be better than 0.1% bupivacaine alone.[1,2]

The oxygen saturation results as noted above showed no difference between the groups, again showing no benefit from the addition of 0.1% bupivacaine. The apparent increase in desaturation occurring during the first postoperative day is likely a result of the patients' being more active and not continuously receiving their supplemental oxygen therapy, a factor we did not attempt to control. When compared with patients receiving epidural morphine, the ten per cent of time that our patients had SpO_2 < 90% is more than has been reported in patients after Caesarean section,[30] but similar to postoperative hysterectomy patients,[31] though none of these patients received supplemental oxygen therapy. As our patients were older and had undergone more radical procedures, withholding oxygen therapy would have been unethical. We did not attempt to determine the aetiology of the desaturation, nor correlate it with the stage of sleep, but only to make comparisons between the two groups of patients for which we found no difference.

In summary, we have shown that in patients having abdominal or thoracic surgery, epidural infusions of fentanyl provide equivalent analgesia from similar infusion rates as do infusions of a mixture of fentanyl and 0.1% bupivacaine. Also there was no difference in the incidence or type of side-effects. Whether epidural infusions of fentanyl and higher concentrations of bupivacaine are synergistic requires further study.

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