Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for post-thoracotomy pain

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Thirty-four patients undergoing thoracotomy were entered into a randomized, double-blind, placebo-controlled study to compare the effects of patient-controlled, lumbar epidural (PCA-E) fentanyl with patient-controlled intravenous (PCA-iv) fentanyl with respect to drug requirements, analgesic efficacy and respiratory function. Prior to chest closure patients received fentanyl $2 \mu\text{g} \cdot \text{kg}^{-1}$ by the epidural or iv route. In the recovery room further doses of epidural or iv fentanyl, $50 \mu\text{g}$, were administered by the patients who controlled two PCA pumps. Background fentanyl infusion rates were increased by $10 \mu\text{g} \cdot \text{hr}^{-1}$ each time the patient administered a drug bolus and were decreased by $10 \mu\text{g} \cdot \text{hr}^{-1}$ whenever visual analogue scale (VAS) pain scores were less than 2 on a maximum 10 scale. Twenty-nine patients completed the study. Patients in the PCA-E group ($n = 14$) required less total fentanyl than those in the PCA-iv ($n = 15$) group ($1857 \pm 693 \mu\text{g}$ vs $2573 \pm 890 \mu\text{g}$ respectively, $P < 0.05$). Fentanyl infusion rates were lower in the PCA-E group at most measurement times. There were no differences between groups in respiratory rates, PaCO_2 , VAS pain scores or changes in pulmonary function as measured by FVC and FEV_1 . It is concluded that satisfactory patient-controlled analgesia can be achieved with both epidural and iv fentanyl after thoracotomy but that fentanyl requirements are

less when given via the epidural route. This supports a direct spinal cord site of action for lumbar epidural fentanyl.

Trente-quatre patients devant subir une thoracotomie ont été évalués dans le cadre d'une étude à double insu, au hasard et avec contrôles placebo afin de comparer les effets du fentanyl épidural contrôlé par le patient (PCA-E) au fentanyl intraveineux contrôlé par le patient (PCA-iv) face au besoin en médicaments, à l'efficacité analgésique et à la fonction respiratoire. Avant la fermeture du thorax, les patients ont reçu $2 \text{ mg} \cdot \text{kg}^{-1}$ de fentanyl par voie épidurale ou intraveineuse. A la salle de réveil, des doses supplémentaires de fentanyl épidural ou intraveineux de $50 \mu\text{g}$ ont été administrées par les patients qui contrôlaient deux pompes PCA. La perfusion de base de fentanyl était augmentée de $10 \mu\text{g} \cdot \text{h}^{-1}$ chaque fois que le patient s'administrerait un bolus de médicament et était diminuée de $10 \mu\text{g} \cdot \text{h}^{-1}$ lorsque les pointages pour la douleur, sur une échelle visuelle analogue (VAS), étaient moins de 2 sur une échelle maximale de 10. Vingt-neuf patients ont complété l'étude. Les patients de groupe PCA-E ($n = 14$) ont nécessité une quantité totale de fentanyl moindre que ceux du groupe PCA-iv ($n = 15$) ($1857 \pm 693 \mu\text{g}$ vs $2573 \pm 890 \mu\text{g}$ respectivement, $P < 0,05$). Les vitesses de perfusion de fentanyl étaient moindre pour le groupe PCA-E à la plupart des mesures. Il n'y avait aucune différence entre les groupes quant aux fréquences respiratoires, PaCO_2 , pointages VAS pour la douleur ou changements de la fonction pulmonaire telle que mesurée par la CVF et la VEMS. En conclusion, une analgésie satisfaisante, contrôlée par le patient, peut être obtenue avec le fentanyl épidural ou intraveineux suite à une thoracotomie, mais les besoins en fentanyl sont significativement moindre lorsque la voie épidurale est employée. Ceci supporte l'action du fentanyl par voie épidurale lombaire à un site sur la moëlle épinière directement.

Key words

ANAESTHETIC TECHNIQUES: epidural, lumbar;
ANALGESIA: postoperative;
ANALGESICS: fentanyl.

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Epidural fentanyl has been investigated in patients undergoing a variety of surgical procedures with conflicting

reports concerning the efficacy of epidural fentanyl compared with systemically administered fentanyl.¹⁻⁷ It has been suggested that epidural fentanyl produces most of its analgesic effects in a systemic manner following vascular uptake from the epidural space.⁵⁻⁷ Other investigations have reported differences in drug requirements, blood levels, and effects on respiratory function.¹⁻³ The respiratory effects of spinal and epidural opioids have been reviewed by Etches *et al.*⁹

To date no published reports have compared patient-controlled *iv* fentanyl (PCA-*iv*) with patient-controlled lumbar epidural fentanyl (PCA-E) following thoracotomy. We therefore carried out a randomized, double-blind, placebo-controlled study to compare the drug requirements and respiratory effects of PCA-E fentanyl with PCA-*iv* fentanyl in patients undergoing posterolateral thoracotomy. We chose to measure drug requirement as the primary variable in order to determine whether or not epidural fentanyl has a direct spinal cord effect; secondary variables studied were Visual Analogue Score (VAS) pain scales, respiratory rates, resting arterial PCO₂, and forced vital capacity (FVC) and forced expiratory volume at one second (FEV₁).

Methods

The study protocol is summarized in Figure 1.

Following approval by the University of British Columbia Screening Committee for Research Involving Human Subjects written, informed consent was obtained from 34 ASA I-III patients scheduled for elective thoracotomy. Patients who were likely to require postoperative mechanical lung ventilation due to severe chronic lung disease were excluded from the study. On the evening before surgery all patients were familiarized with a dual PCA pump system and with a standard vertical 10 cm VAS pain scale (0 = "no pain," 10 = "worst possible pain").

Patients were premedicated with oral diazepam 10 mg. In the operating room a peripheral *iv* catheter and radial artery catheter were placed following local anaesthetic infiltration. An epidural catheter was placed at the L₁₋₂ or L₂₋₃ interspace using a loss of resistance to saline technique. A test dose of 3 ml bupivacaine 0.5% with epinephrine 5 µg · ml⁻¹ was administered to rule out intravascular or subarachnoid placement of the catheter. No other epidural local anaesthetics were administered throughout the study.

Anaesthesia was induced with fentanyl 3-5 µg · kg⁻¹ and thiopentone 2-4 mg · kg⁻¹. Muscle relaxation was achieved with pancuronium and the trachea was intubated with a left-sided disposable double-lumen tube. All patients had in-dwelling bladder catheters placed after the induction of anaesthesia. Anaesthesia was maintained with isoflurane 0-1.5% end tidal, oxygen, air, and further

FIGURE 1 Summary of study protocol.

increments of fentanyl *iv* to a maximum total dose of 10 µg · kg⁻¹. No *iv* fentanyl was administered in the last hour of the procedure.

Patients were randomized into PCA-*iv* and PCA-E groups. During closure of the chest all patients received both epidural and *iv* injections. Patients in the PCA-E group received fentanyl 2 µg · kg⁻¹, concentration 10 µg · ml⁻¹, via the epidural catheter and an equal volume of saline *iv*. The PCA-*iv* patients received fentanyl 2 µg · kg⁻¹ *iv*, concentration 10 µg · ml⁻¹, and an equal volume of epidural saline. The tracheas of all patients were extubated in the operating room at the end of surgery.

In the recovery room PCA pumps (Abbott Life Care PCA Plus-4100, Abbott Laboratories) capable of delivering boluses and continuous infusions were connected to both the epidural catheter and a peripheral *iv*. In the PCA-E group the epidural pump contained fentanyl 10 µg · ml⁻¹ and the *iv* pump contained saline; these were reversed in the PCA-*iv* group. The pumps were set to deliver fentanyl by infusion at 0.75 µg · hr⁻¹ initially. When the patient desired increased analgesia the pumps were activated with two remote control buttons which delivered fentanyl 50 µg from one pump and an equal volume of saline from the other. The lockout interval was set at 15 min. Each time a PCA bolus was administered, the infusion rate from both pumps was increased by 10 µg · kg · hr⁻¹ by the nursing staff to a maximum of 150 µg · hr⁻¹ (or 2.0 µg · kg⁻¹ · hr⁻¹ in patients less than 75 kg). The objective was to achieve a level of analgesia where the patients did not require frequent PCA boluses.

The VAS pain scores were measured every two hours both at rest and with vigorous coughing. Whenever a

FIGURE 2 Fentanyl infusion rates for PCA-E and PCA-iv patients measured at three-hour intervals after admission to the recovery room. Results are mean $\pm$ SD.

TABLE I Patient characteristics, fentanyl requirements and side-effects – mean (SD)

Characteristics	PCA-E	PCA-iv
Male/female	10/4	9/6
Age (yr)	55.9 (11.7)	55.7 (10.6)
Height (cm)	173.7 (10.4)	170.5 (9.3)
Weight (kg)	73.5 (13.9)	77.6 (18.7)
Procedures:		
– Lobectomy	7	6
– Bilobectomy	–	1
– Pneumonectomy	1	3
– Other	6	5
Total fentanyl post-op (μ g)	1857 (693)	2573 (890)
Nausea/vomiting	5/14	4/15
Pruritis	0/14	2/15

patient's VAS score was less than 2 at rest the iv and epidural infusion rates were decreased by $10 \mu\text{g} \cdot \text{hr}^{-1}$ in an effort to achieve the lowest possible infusion rates that maintained analgesia.

All patients received supplemental oxygen, 35% to 50% by face mask. Respiratory rates were recorded hourly, arterial oxygen saturation was monitored continuously by pulse oximetry and blood gases measured every three hours. The patient's FVC and FEV₁ were measured in a sitting position the morning after surgery (Vitalograph R, Vitalograph Medical Instruments) and were compared to preoperative values measured in the pulmonary function laboratory. Pruritus, nausea, vomiting and urticaria were noted by the nursing staff but the severity of these side-effects was not quantitated.

Data were collected for at least 20 hr in all patients who completed the study. Results are expressed as mean $\pm$ SD. Demographic variables were compared using unpaired

FIGURE 3 VAS pain scores for PCA-E and PCA-iv patients measured during quiet breathing at two-hour intervals after admission to the recovery room. Results are mean $\pm$ SD.

TABLE II Spirometry – mean (SD)

	PCA-E	PCA-iv
Pre-op FVC (L)	4.19 (1.32)	3.78 (1.43)
Post-op FVC (L)	1.67 (0.64)*	1.52 (0.70)*
Pre-op FEV ₁ (L)	3.26 (1.21)	2.64 (1.05)
Post-op FEV ₁ (L)	1.21 (0.49)*	1.48 (1.09)*

*Significantly less than preop. $P < 0.05$.

Student's *t* tests. The total amounts of fentanyl received by each group were also compared with unpaired Student's *t* tests. Fentanyl infusion rates, VAS scores, and respiratory variables were all analyzed with two-factor ANOVA with repeated measures on the time factor. Post hoc comparisons were done where applicable using Neuman-Kuels Test.

Results

Twenty-nine patients completed the study, 14 in the PCA-E group and 15 in the PCA-iv group. One patient in the PCA-iv group was withdrawn due to inadequate pain relief in spite of receiving fentanyl $250 \mu\text{g} \cdot \text{hr}^{-1}$. Two additional patients were returned to the operating room for control of intrathoracic bleeding and were therefore eliminated from the study as was a fourth patient who underwent a more extensive procedure than planned, including chest wall resection with mesh reconstruction. A fifth patient was returned to the ward before data collection was complete due to demands on the intensive recovery area.

Demographic data, total fentanyl requirements and the incidence of side-effects associated with fentanyl are summarized in Table I. There were no differences in patient characteristics or in the types of procedure performed. The PCA-E patients required less total fentanyl

FIGURE 4 VAS pain scores for PCA-E and PCA-iv patients measured during vigorous coughing at two-hour intervals after admission to the recovery room. Results are mean $\pm$ SD.

FIGURE 5 Arterial PCO₂ levels for PCA-E and PCA-iv patients measured every three hours after admission to the recovery room. Results are mean $\pm$ SD.

than did PCA-iv patients ($1857 \pm 693 \mu\text{g}$ and $2573 \pm 890 \mu\text{g}$ respectively, $P < 0.05$). Fentanyl infusion rates were higher in the PCA-iv group at one, three, six, nine and twelve hours postoperatively (Figure 2).

The incidence of side-effects was similar in the two groups. The incidence of urinary retention could not be measured as all patients had Foley catheters as part of their routine management. The VAS data are shown in Figures 3 and 4. Pain scores were similar at all times except at 6 and 14 hours postoperatively when VAS at rest were lower in the PCA-E group.

There were no differences between groups in resting arterial PCO₂ levels (Figure 5) or in respiratory rates (Figure 6) throughout the study period. None of the patients in either group had an arterial oxygen saturation of less than 90% at any time.

FIGURE 6 Respiratory rates for PCA-E and PCA-iv patients recorded every two hours after admission to the recovery room. Results are mean $\pm$ SD.

The changes in spirometry before and after surgery are summarized in Table II; there was a decrease in FVC and FEV₁, after operation in each group ($P < 0.05$) but no difference between groups at either measurement time.

Discussion

Previous investigators have reported conflicting results concerning the efficacy of epidural fentanyl compared with *iv* or intramuscular (*im*) fentanyl in patients undergoing a variety of surgical procedures.¹⁻⁸ The lack of consistent findings in these studies may be related to several factors including the use of widely different concentrations of fentanyl in the epidural space, the potential for subjective observer bias in assessing patient pain and in determining when boluses of fentanyl were administered, and a failure to attempt to reduce fentanyl infusion rates once analgesia was achieved.

The primary purpose of this study was to determine whether lumbar epidural fentanyl was more effective than *iv* fentanyl in the management of post-thoracotomy pain. We chose fentanyl requirement as the primary indicator of drug effectiveness. The VAS scores were measured frequently, but in a protocol where analgesia was available on a patient-controlled basis it was anticipated that there would be no differences between groups in VAS scores. We used the same concentration of epidural fentanyl in all patients, $10 \mu\text{g} \cdot \text{ml}^{-1}$, which has been shown by Welchew to be the optimal concentration for fentanyl administered at the T₇₋₈ interspace for pain following upper abdominal surgery.¹⁰ The administration of fentanyl boluses and subsequent adjustment of fentanyl infusions were done on a blinded, patient-controlled basis thereby eliminating possible bias on the part of the recovery room nursing staff. Lastly, once the patient was comfortable we sought

to determine the lowest infusion rates that maintained acceptable analgesia.

We found that patients in the PCA-E group required less fentanyl than patients in the PCA-iv group over a 20-hr study period. There were no differences between groups in the adequacy of analgesia as assessed by VAS or in respiratory rates and resting PaCO₂ levels. Both groups had similar decreases in FVC and FEV₁ following thoracotomy.

Our results are consistent with those of Lomessy *et al.* who found in a crossover design study that fentanyl 200 µg as a single bolus was more effective given in the lumbar epidural space than when administered *im* for reducing pain after abdominal or thoracic surgery.³ Justins *et al.* also found that epidural fentanyl 200 µg produced more effective analgesia with more rapid onset than fentanyl 200 µg *im* in patients in the first stage of labour.² Plasma fentanyl concentrations increased more slowly and reached lower peak levels in the epidural group as was the case in a report by Negre *et al.*¹

Ellis *et al.*, on the other hand, reported similar fentanyl requirements, analgesic effectiveness, and plasma fentanyl concentrations in their study of epidural vs *iv* fentanyl given by infusion post-Caesarean section pain.⁶ These authors employed various concentrations of fentanyl ranging from 3.8–7.5 µg · ml⁻¹. Fentanyl concentrations of less than 10 µg · ml⁻¹ have been shown to produce less satisfactory analgesia.¹⁰ Boluses of fentanyl, when required, were administered by one of the investigators rather than on a patient-controlled basis as in our study.

Loper *et al.* could not demonstrate any difference in fentanyl requirements, VAS pain scores or plasma fentanyl levels when they compared epidural with *iv* fentanyl infusions after knee ligament reconstruction.⁵ Their protocol, however, employed fentanyl 50 µg · ml⁻¹ at 2 ml · hr⁻¹ *iv* or through a L₂₋₃ or L₃₋₄ epidural catheter; the small volumes of epidural fentanyl administered may have been inadequate to reach the L₂₋₃ spinal cord segments, located at the T₁₂ vertebral body, and would therefore not produce a direct spinal cord effect.

Welchew and Breen recently reported results similar to ours in their study of fentanyl administered via a thoracic epidural catheter compared with fentanyl administered *iv* in patients who had undergone upper abdominal surgery.⁸ Fentanyl was delivered in a patient-controlled basis; patients in the epidural group required significantly less fentanyl than patients in the *iv* group over a 24-hr study period. Pain scores were similar between groups as was the case in our study.

Panos *et al.* and Stringer *et al.* have reported their preliminary findings comparing lumbar epidural fentanyl to *iv* fentanyl following thoracotomy.¹⁰⁻¹¹ They could not demonstrate any difference in drug requirements, plasma

concentrations, VAS pain scores or respiratory effects in a small number of patients. Fentanyl concentrations were not reported, however, and no attempts were made to reduce fentanyl infusion rates after the patients were comfortable.

Shulman *et al.* showed that epidural morphine was more effective than *iv* morphine in preserving post-thoracotomy pulmonary function as measured by FEV₁ and FVC at two and 24 hr postoperatively.¹² We were unable to demonstrate a similar benefit in our PCA-E patients who had reductions in FEV₁ and FVC equal to patients in the PCA-iv group. The reason for the discrepancy between our findings and those of Shulman *et al.* is not apparent.

In summary we found that both *iv* and lumbar epidural fentanyl, when given on a patient-controlled basis following thoracotomy, produced similar levels of analgesia with similar effects on respiratory rates, resting PCO₂ and pulmonary function. Patients in the epidural group required significantly less fentanyl, however, suggesting that lumbar epidural fentanyl has a direct analgesic effect on the spinal cord extending to the upper thoracic segments.

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