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A Randomized Double-blind Comparison of Epidural versus *Intravenous Fentanyl Infusion for Analgesia after Thoracotomy*

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This study compared epidural and intravenous fentanyl infusions for pain relief for the first 20 h after thoracotomy, in order to examine whether an thoracic epidural fentanyl infusion offers clinical advantage over an intravenous infusion. Forty patients were assigned randomly to receive either fentanyl epidurally and saline intravenously or fentanyl intravenously and saline epidurally in a double-blind fashion. For each patient the fentanyl infusion was titrated to a rate required for pain relief (pain score < 3, maximum 10). Patients reported similar median pain scores, but in the epidural group the required mean fentanyl infusion rate was less (0.95 ± 0.23 *vs.* 1.67 ± 0.46 $\mu g \cdot kg^{-1} \cdot h^{-1}$, $P = 0.0001$) and plasma fentanyl concentrations were less at 4 and 18 h (4 h: 0.81 ± 0.27 *vs.* 1.38 ± 0.36 $ng \cdot ml^{-1}$, $P = 0.0001$; 18 h: 0.94 ± 0.32 *vs.* 1.54 ± 0.65 $ng \cdot ml^{-1}$, $P = 0.0007$) than those in the intravenous group. Respiratory function was better preserved and the incidence of nausea and sedation was less in the epidural group than in the intravenous group. In conclusion there appears to be a clinical advantage to the epidural infusion over the intravenous infusion of fentanyl for analgesia after thoracotomy. (Key words: Analgesia, postoperative. Analgesics, epidural: fentanyl. Analgesics, intravenous: fentanyl. Anesthetic techniques, epidural.)

THE VALUE of epidurally administered opioids in the relief of postoperative pain is now well established.[1,2] Epidural fentanyl is known to produce a rapid, intense, but brief analgesic action, which can be prolonged by a continuous infusion.[3–7] Fentanyl administered by continuous intravenous infusion has also been used for postoperative analgesia.[8–11] There are conflicting reports about the efficacy of epidural fentanyl when compared with systemically administered fentanyl. Two recent studies could not demonstrate any clinical advantage to epidural infusion over intravenous infusion of fentanyl for postoperative analgesia.[12,13] However Lomessy *et al.*[4] reported greater plasma concentrations of fentanyl but less intense analgesic after intramuscular fentanyl injection than after epidural fentanyl injection, and van der Hoogen *et al.*[14] have reported in their animal studies a 2–3.8-fold potency gain and a greater specificity of fentanyl administered epidurally compared to systemic administration.

Pain after thoracotomy is considered to be among the most severe postoperative pain, and analgesia may be difficult to achieve without also incurring severe side effects.[15] This study compared the effect of epidural and intravenous fentanyl infusions upon analgesia and the incidence and severity of side effects in patients following thoracotomy. Our hypothesis was that it is possible to achieve equal relief from pain and less respiratory depression by administering fentanyl epidurally than by administering it intravenously.

Materials and Methods

The study protocol was approved by the Hospital Research Ethics Committee and informed written consent was obtained from all patients. Forty adult patients, ASA physical status 1–3, who were scheduled for elective thoracotomy and who had no contraindications to epidural anesthesia, were randomly allocated to one of two groups, intravenous or epidural. For 20 postoperative hours patients in the intravenous group received fentanyl intravenously and saline epidurally; those in the epidural group received fentanyl epidurally and saline intravenously. Patients, nurses, surgeons, anesthesiologists, and investigators were blinded to the route of fentanyl administration.

All patients received a standardized anesthesia. The epidural catheter was introduced between the forth or fifth thoracic interspace using a paramedian approach and loss-of-resistance technique. An epidural test dose of 3–4 ml 0.5% bupivacaine was administered and the block was tested 15 min later. Anesthesia was induced by intravenous fentanyl (2 $\mu g \cdot kg^{-1}$) and intravenous thiopental 3–5 $mg \cdot kg^{-1}$ followed by pancuronium (0.08 $mg \cdot kg^{-1}$). Anesthesia was maintained with 50–66% nitrous oxide in oxygen and pancuronium (0.02 $mg \cdot kg^{-1}$), and 0.5–1.5% enflurane was added if necessary for blood pressure control. Analgesia was controlled by giving intravenous fentanyl 2 $\mu g \cdot kg^{-1}$ before skin incision and 1 $\mu g \cdot kg^{-1}$ thereafter every 20 min. Patients' lungs were ventilated mechanically during the operation (arterial carbon dioxide tension [Pa_{CO_2}] 37–40 mmHg). At the end of the surgery residual neuromuscular blockade was reversed with a mixture of glycopyrrolate and neostigmine. Following tracheal extubation the patients received 28% oxygen *via* air-entrainment oxygen mask.

The concentration of intravenous fentanyl for postoperative pain relief was 50 $\mu g \cdot ml^{-1}$. Epidural fentanyl was diluted in 0.9% saline to a concentration of 12.5 $\mu g \cdot ml^{-1}$. Solutions were prepared and coded by a nurse not involved in the study or patient care.

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After arrival in the intensive care unit the patients in the intravenous group received a fentanyl bolus of 25 μg (0.5 ml) and a fentanyl infusion at 75 $\mu g \cdot h^{-1}$ (1.5 $ml \cdot h^{-1}$) through an intravenous catheter. Simultaneously a saline bolus of 6 ml was given, and a saline infusion at 3 $ml \cdot h^{-1}$ was started *via* the epidural catheter. If the patient did not report pain the infusions were started without giving the boluses.

The patients in the epidural group received a fentanyl bolus of 75 μg (6 ml) and a fentanyl infusion at 37.5 $\mu g \cdot h^{-1}$ (3 $ml \cdot h^{-1}$) through the epidural catheter. Concurrently a bolus of saline 0.5 ml was administered and an intravenous saline infusion at 1.5 $ml \cdot h^{-1}$ was started *via* an intravenous catheter. If the patient did not report pain the infusions were started without giving the boluses.

Patients' pain was evaluated every 20 min by one of the investigators (T.S.) or by a trained nurse, and the patients received boluses of 0.5 ml intravenously and 2 ml epidurally if the visual pain scale (VPS) score was not < 3. Simultaneously, the intravenous infusion rate was increased by 0.5 $ml \cdot h^{-1}$ and epidural infusion rate by 1 $ml \cdot h^{-1}$. Thus patients in the intravenous group received a bolus of 25 μg fentanyl intravenously, and the intravenous infusion rate was increased by 25 $\mu g \cdot h^{-1}$. In the epidural group patients were given a bolus of 25 μg fentanyl epidurally, and the epidural infusion rate was increased by 12.5 $\mu g \cdot h^{-1}$. This adjustment was repeated every 20 min until the VPS score was <3. Maximal infusion rates were 150 $\mu g \cdot h^{-1}$ (3 $ml \cdot h^{-1}$) intravenously and 75 $\mu g \cdot h^{-1}$ (6 $ml \cdot h^{-1}$) epidurally, but it was possible to give an extra 25 μg bolus of fentanyl intravenously or epidurally every 20 min for further pain relief. If the patient's respiratory rate per minute was less than 10 or the patient was asleep and aroused with difficulty or patient's pain was controlled (VPS < 3) for a period of 4 h, the infusion rate was incrementally decreased one step every hour: intravenous infusion by 0.5 $ml \cdot h^{-1}$ (25 $\mu g \cdot h^{-1}$) and epidural infusion by 1 $ml \cdot h^{-1}$ (12.5 $\mu g \cdot h^{-1}$). No other analgesic or sedatives were administered during the study.

The VPS score, respiratory rate, blood pressure, heart rate, somnolence score, and presence of nausea, urinary retention, and pruritus were recorded every 20 min until the patients were comfortable (VPS < 3) and after that every hour for 20 postoperative hours. One of the investigators (T.S.) estimated the pain scores of those patients, who were not alert enough immediately after the arrival in the intensive care unit to assess their pain using the VPS.

Postoperative pain was evaluated using two methods: VPS and a pain relief questionnaire. The VPS was sigmoid-shaped with five facial expressions for different degrees of pain presented by El-Baz *et al.*[16] Pain scores were from 0 to 10 (0 = no pain and 10 = severe pain, *i.e.*, worst pain imaginable). Patients assessed their incisional pain when breathing normally. At end of the study each patient was asked to evaluate subjectively the efficacy of the pain control using a verbal pain relief score of excellent, good, fair and poor pain relief (pain relief questionnaire).

Respiratory rate of < 10 breaths per min was defined as slow respiratory rate. Arterial blood gases were measured 30 min and 4, 10, and 16 h after arrival to the intensive care unit and on the first postoperative morning. Respiratory insufficiency was scored from 0 to 2: 0 = not clinically significant, (Pa_{CO_2} < 53 mmHg); 1 = no clinical signs or symptoms (Pa_{CO_2} > 53 mmHg); 2 = severe respiratory insufficiency with or without apnea requiring immediate treatment. Possible atelectasis in postoperative x-rays was recorded.

Patients' somnolence was evaluated on a scale of 1–4: 1 = wide awake; 2 = dozing; 3 = asleep but easily aroused; and 4 = asleep and aroused with difficulty. The severity of nausea was graded by the investigators: 0 = none; 1 = mild nausea; 2 = moderate nausea requiring treatment (droperidol 1.25 mg intravenously); 3 = vomiting. Pruritus was recorded when reported by patients.

Urinary retention was evaluated on a scale of 0–3: 0 = none; 1 = one in-and-out bladder catheterization needed; 2 = two in-and-out bladder catheterizations; 3 = a Foley catheter required.

Plasma concentrations of fentanyl were measured at 4 and 18 h postoperatively. Blood for these measurements was obtained from the radial artery catheter; the plasma was heparinized, centrifuged, and stored at −20° C until analyzed by radioimmunoassay by the Bioanalytical Laboratory of Janssen Pharmaceutica. The lowest detection limit for the assay is 0.1 $ng \cdot ml^{-1}$.

The data were analyzed using Wilcoxon's rank sums

TABLE 1. Patient Group Characteristics

	Intravenous Fantanyl	Epidural Fentanyl
Age (yr)	57 ± 11	63 ± 10
Male/female	13 ≠ 7	15 ≠ 5
Weight (kg)	71 ± 12	71 ± 13
Height (cm)	166 ± 7	167 ± 6
Preoperative pulmonary disease	9 (45%)	13 (65%)
Surgery		
Pneumectomy	3 (15%)	4 (20%)
Lobectomy	14 (70%)	11 (55%)
Diagnostic thoractomy	3 (15%)	5 (25%)
Duration of operation (min)	121 ± 31	120 ± 62
Blood loss (ml)		
Intraoperative	465 ± 397	357 ± 276
Postoperative	501 ± 218	548 ± 413
Intraoperative fentanyl dose (μg/kg)	7.4 ± 1.56	8.22 ± 2.92

Values are number of patients or units shown, mean ± SD.
The differences are not significant.

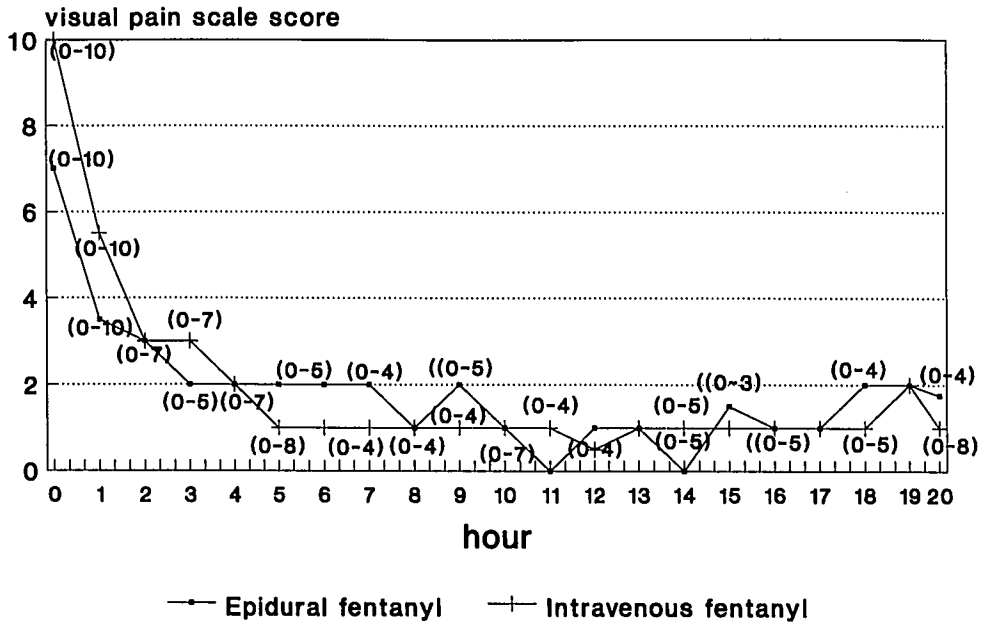

FIG. 1. The visual pain scores recorded at each postoperative hour in both groups (median and range). The differences were not significant.

(pain scores, mean fentanyl infusion rates, fentanyl plasma concentrations, and blood pressure), Fisher's exact test (two-tail) (pain questionnaire, respiratory insufficiency, atelectasis, somnolence, nausea, and urinary retention), and chi-squared analysis (slow respiratory rate). The data of Pa_{CO_2}, arterial oxygen tension (Pa_{O_2}), mean heart rate, and mean respiratory rate were compared between groups using a repeated-measures multivariate analysis of variance. $P < 0.05$ was considered significant. The data are presented as means ± standard deviations and 95% confidence intervals of group mean differences. Pain scores are presented as median and range.

Results

Twenty patients were assigned to each group. The groups were similar for age, weight, height, the incidence of preoperative pulmonary disease (chronic productive cough, preoperative $Pa_{O_2} < 75$ mmHg), the duration and type of operation, intra- or postoperative blood loss, and fentanyl dose during operation (table 1).

Figure 1 shows VPS scores (median and range) in both groups at each hour during the first 20 postoperative hours. The VPS scores and pain relief questionnaire scores were similar in both groups, and patients were quite pleased with their pain control (table 2).

Figure 2 shows the cumulative fentanyl dose in the two groups at every hour during the study. The postoperative fentanyl requirements per hour (micrograms per kilogram per hour) were larger in the intravenous group than in the epidural group during 0–4 h ($P = 0.0001$, 95% confidence intervals = 0.67–1.61) and during 4–20 h ($P = 0.0001$, 95% confidence intervals = 0.43–0.87) (table 2). The plasma concentrations of fentanyl (nanograms per milliliter) were less in the epidural group at 4 h ($P = 0.0001$, 95% confidence intervals = 0.34–0.79) and at 18 h ($P = 0.0007$, 95% confidence intervals = 0.28–0.93) than in the intravenous group (table 2).

Mean postoperative Pa_{CO_2} was greater in the intravenous group than in the epidural group (fig. 3), but mean respiratory rates were similar in both groups. The incidence of slow respiratory rate was 40% in the intravenous group and 15% in the epidural group ($P = 0.08$). In the intravenous group 50% of patients had $Pa_{CO_2} > 53$ mmHg and 15% (3 patients) had severe insufficiency or an apneic episode. In the epidural group 10% of patients (two) had $Pa_{CO_2} > 53$ mmHg at least once but none of these patients

TABLE 2. Pain, Dose, and Concentration

	Intravenous Fentanyl	Epidural Fentanyl	P
Pain relief questionnaire (at 20 h)			0.25
Excellent	9 (45.0%)	4 (21.3%)	
Good	10 (50.0%)	12 (63.2%)	
Fair	1 (5.0%)	3 (15.5%)	
Poor	0 (0.0%)	0 (0.0%)	
Postoperative fentanyl dose ($\mu g \cdot kg^{-1} \cdot h^{-1}$)			
0–4 h	2.41 ± 0.99	1.27 ± 0.31	0.0001
4–20 h	1.50 ± 0.41	0.85 ± 0.26	0.0001
0–20 h	1.67 ± 0.46	0.95 ± 0.23	0.0001
Postoperative plasma fentanyl (ng/ml)			
4 h	1.38 ± 0.36	0.81 ± 0.27	0.0001
18 h	1.54 ± 0.65	0.94 ± 0.32	0.0007

Values are number of patients or units shown, mean ± SD.

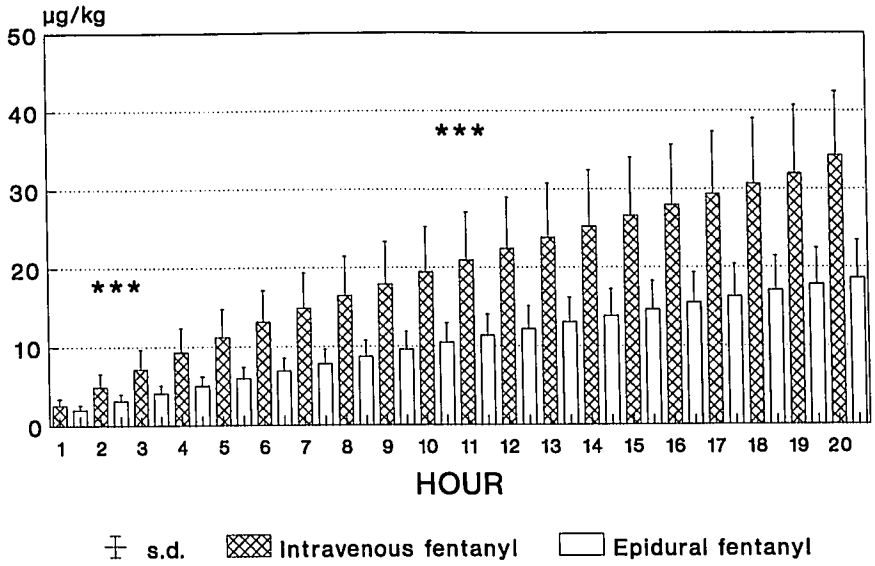

FIG. 2. The cumulative fentanyl dose (micrograms per kilogram) at each postoperative hour in both groups. The differences between groups for mean fentanyl infusion doses at 0–4 and 4–20 h both were statistically significant. ***$P = 0.0001$.

had severe respiratory insufficiency (table 3). There was no decrease in blood pressure, and heart rates were similar in both groups. The occurrence of somnolence, nausea, pruritus, urinary retention, and atelectasis is presented in table 3. The patients in the intravenous group were drowsy or asleep a longer time than were patients in the epidural group ($P = 0.02$). In the intravenous group 50% of patients had nausea and 15% vomited whereas only 20% of the patients in the epidural group had mild nausea ($P < 0.001$). Urinary retention was a common side effect in both groups. Only two patients, one in the intravenous group and one in the epidural group, reported mild pruritus. Five patients (25%) in both groups had minor radiologically verified atelectasis during the first 20 postoperative hours. Postoperative Pa_{O_2} was comparable in both groups (64–90 mmHg).

Discussion

Our objective was to compare the efficacy and safety of intravenous and epidural fentanyl infusions after major surgery by providing equianalgesia and then assessing fentanyl dose requirements, plasma fentanyl concentrations, and side effects. Although postoperative pain after thoracotomy can be very severe and difficult to control, it was possible to accomplish good and equal pain relief in both groups. In the epidural group the required mean fentanyl infusion rate was less and plasma fentanyl concentrations were less than those in the intravenous group, showing the superior efficacy of epidural fentanyl over intravenous fentanyl infusions. We began postoperative pain management with a fentanyl infusion rate titrated in a double-blind fashion to the point where each pa-

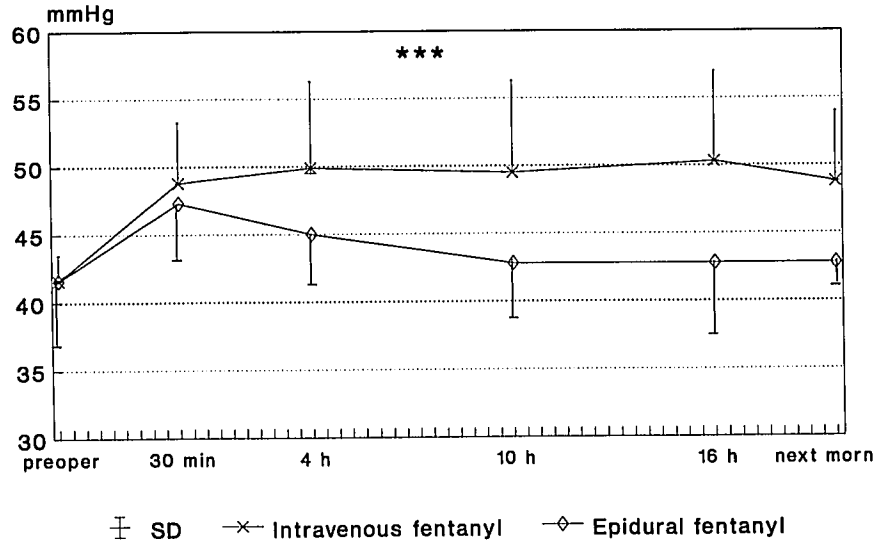

FIG. 3. Pre- and postoperative Pa_{CO_2} (30 min and 4, 10, and 16 h after surgery and the next morning). The difference between the groups was statistically significant. ***$P < 0.002$.

TABLE 3. Side Effects

Side Effect	Intravenous Fentanyl	Epidural Fentanyl	P
Respiratory rate <10 breaths per min	8 (40%)	3 (15%)	0.08
Respiratory insufficiency			<0.001
Pa_{CO_2} > 53 mmHg	10 (50%)		
Severe or apnea	3 (15%)	2 (10%)	
Somnolence: time drowsy or asleep (h, mean ± SD)	7.7 ± 4.3	4.7 ± 3.7	0.02
Nausea: mild/vomiting	13 (65%)	4 (20%)	<0.001
Pruritus	1 (5%)	1 (5%)	1.0
Urinary retention	9 (47%)	11 (58%)	0.16
Atelectasis	5 (25%)	5 (25%)	1.0

tient was comfortable (VPS < 3). The infusion rate limits for fentanyl were established according to published data.[5,6,8–11,17–19] The intravenous infusion rate of 1.67 ± 0.46 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the epidural infusion rate of 0.95 ± 0.23 $\mu g \cdot kg^{-1} \cdot h^{-1}$ needed to achieve good analgesia in our patients were reasonably similar to rates reported by other investigators.[5,8–11,17–19]

Plasma fentanyl concentrations in our intravenous group were similar to concentrations from previous investigations, with good pain relief after intravenous infusion of fentanyl.[8,10–12] The reported plasma fentanyl concentrations after epidural infusion have varied widely, from undetectable to 4.7 $ng \cdot ml^{-1}$.[3,5,13,17,18] In these studies the infusion rate of fentanyl was usually constant. In the study by Ellis *et al.* the epidural fentanyl infusion rate for pain relief after cesarean section was adjusted according to need.[13] The plasma fentanyl concentration in their study at 24 h (0.93 ± 0.29 $ng \cdot ml^{-1}$) is near the concentration in our study at 18 h (0.94 ± 0.32 $ng \cdot ml^{-1}$), although pain after cesarean section (lower abdominal operation) is of lesser magnitude.[15] The reason for their high fentanyl concentrations may be related to the inadequacy of lumbar epidural administration for cesarean section pain.

To date there are two other controlled clinical studies comparing pain relief and plasma fentanyl concentrations following continuous intravenous and epidural fentanyl infusions.[12,13] Loper *et al.* gave fentanyl 100 $\mu g \cdot h^{-1}$ (50 $\mu g \cdot ml^{-1}$) either intravenously or epidurally to 20 patients after anterior cruciate ligament repair.[12] There were no significant differences in pain scores at 18 h postoperatively, in the number of supplemental analgesic boluses, in plasma fentanyl concentrations, or in the incidence of side-effects. The investigators concluded that continuous epidural fentanyl offers no clinical advantages over continuous intravenous infusion. Loper *et al.*[12] administered fentanyl at a constant rate of 100 $\mu g \cdot h^{-1}$ with possible supplemental analgesic boluses (50 μg [2 ml] fentanyl) both intravenously and epidurally, whereas we started with lower infusion rates (75 $\mu g \cdot h^{-1}$ intravenously and 37.5 $\mu g \cdot h^{-1}$ epidurally) and ultimately administered different mean infusion rates for the intravenous group (> 100 $\mu g \cdot h^{-1}$) and for the epidural group (<100 $\mu g \cdot h^{-1}$). In the study by Loper *et al.*[12], the concentration of the epidural fentanyl infusion was high (50 $\mu g \cdot ml^{-1}$) although it has been shown that increasing the volume of diluent produces a significantly more rapid onset and larger duration of analgesia.[20,21]

Ellis *et al.* compared intravenous and lumbar epidural fentanyl infusions after cesarean section.[13] The severity of side effects and end-tidal carbon dioxide concentration were similar for both groups. The plasma concentrations of fentanyl at 12 h but not at 24 h were less in the epidural group. In this study by Ellis *et al.*[13] there were, however, three patients in the intravenous group who were eliminated from the study because of inadequate pain relief despite the maximum allowable infusion rate of 2.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$. If these three patients, who consisted 25% of original intravenous group, had not been eliminated from statistical analysis the outcome might have been different.

We conclude that in order to demonstrate a potency gain with epidural fentanyl, it is important to adjust the dose according to need, to place the catheter tip closer to the painful dermatomes (thoracic catheter for thoracic operations, since lipophilic agents have difficulty migrating in the spinal fluid), and to use adequate diluent.[20–22] In our study, respiratory depression was a frequent side effect in the intravenous group. Like Holley and Van Steennis[10] (125 $\mu g \cdot h^{-1}$) we found that intravenous fentanyl produced an unacceptable incidence of severe respiratory depression. Two patients (10%) in our epidural group had a Pa_{CO_2} > 53 mmHg at least once, but none of them developed severe respiratory depression. Ahuja and Strunin found no significant change in Pa_{CO_2} after a bolus of 1.5 $\mu g \cdot kg^{-1}$ epidural fentanyl followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 18 h.[18] In the study by Renaud *et al.* epidural fentanyl was given by a bolus dose of 1 $\mu g \cdot kg^{-1}$, followed by a continuous infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over 18 h. They examined the slope of ventilatory response to carbon dioxide and found moderate ventilatory depression of no demonstrable clinical consequence.[17] In our study the mean epidural fentanyl infusion rate, 0.95 ± 0.23 $\mu g \cdot kg^{-1} \cdot h^{-1}$, produced respi-

ratory depression of no evident clinical significance, but only a small number of patients were studied, and more profound respiratory depression occasionally may occur.[23]

The relationship between somnolence and analgesia is complex. Inadequate pain relief may cause sleep disturbances, with more time spent awake. Conversely, if excessive sedation accompanies good pain control, more time is spent asleep. Ellis *et al.* found that patients after cesarean section were either dozing or asleep most of the time but easily aroused whether they were in the intravenous or epidural group.[13] In our study the groups did not differ in pain relief, but the intravenous group spent significantly more time asleep or drowsy.

Urinary retention is most common after major surgery, and its incidence increases with age.[24] In our study the urinary retention occurred so frequently that prophylactic catheterization of the bladder is indicated using these methods of pain relief after thoracotomy.

Unfortunately the pain scores we measured are rest scores, and we do not have data during coughing. Not negating the value of data on pulmonary function (forced vital capacity and peak expiratory flow), we studied only the incidence of pulmonary morbidity of our patients: five patients (25%) in both groups had minor atelectasis during the first 20 postoperative hours.

In summary, we found that fentanyl produces effective analgesia of comparable quality when infused either intravenously or epidurally, but that epidurally administered fentanyl required a lower dose and serum concentration compared to those with intravenous administration. Respiratory function was better preserved and the incidence of nausea and sedation was less in the epidural group than in the intravenous group.

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