

A Randomized Double-Blind Comparison of Epidural Versus Intravenous Fentanyl Infusion for Analgesia after Cesarean Section

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The authors conducted a randomized double-blind controlled study comparing groups of patients receiving iv or epidural fentanyl infusions to determine whether, at comparable levels of analgesia, 1) the severity of side effects was different; and 2) plasma fentanyl concentrations differed between the two groups. Twenty-eight ASA physical status 2 women scheduled to undergo elective cesarean section were randomized into two groups to either receive fentanyl intravenously and saline epidurally or fentanyl epidurally and saline intravenously. After delivery of the infants under epidural anesthesia, each patient received a bolus of fentanyl 1.5 $\mu\text{g}/\text{kg}$ either intravenously or epidurally, and a fentanyl infusion was begun *via* the same route. Concurrently, a saline bolus and infusion were given *via* the alternate route. The rates of the fentanyl and saline infusions were adjusted until each patient was comfortable. Patients rated their pain, nausea, and pruritus on visual analogue scales. Sedation was evaluated by an observer. Respiratory depression was evaluated by end-tidal P_{CO_2} . Data were analyzed by unpaired two-tail *t* tests. Plasma fentanyl concentrations were measured at 12 and 24 h. Three patients in the iv group were dropped from the study because of inadequate pain relief. For the remaining 25 patients, similar infusion rates of fentanyl were required to produce similar levels of analgesia at 12 and 24 h. The severity of nausea, pruritus and sedation, and end-tidal P_{CO_2} were similar for both groups. The plasma concentrations of fentanyl were significantly greater in those who received iv fentanyl at 12 h but not at 24 h. In conclusion, there appears to be no clinical advantage to epidural infusion over iv infusion of fentanyl for analgesia after cesarean section. (Key words: Analgesia, postoperative. Analgesics, epidural: fentanyl. Analgesics, intravenous: fentanyl. Anesthesia, obstetric: cesarean section. Anesthetic techniques, epidural. Complications: nausea; pruritus; respiratory depression; sedation.)

EPIDURAL OPIOID administration has been advocated for providing excellent postoperative analgesia. This high quality of pain relief may carry with it some disadvantages, such as respiratory depression and annoying side effects. Epidural fentanyl is known to produce excellent pain relief with minimal risk of respiratory depression. However, when the duration of action is prolonged by continuous infusion into the epidural space, the dose required to achieve analgesia may be similar to that used for iv infusion^{1,2} and systemic side effects such as nausea, pru-

ritus, and sedation have been noted.³ Because the doses required epidurally may be similar to those for im or iv administration, and because the plasma concentrations after epidural fentanyl may approach those associated with analgesia after im or iv administration,¹⁻⁴ it is not known whether that epidural fentanyl acts predominantly at the spinal cord level or *via* supraspinal mechanisms following systemic uptake. Therefore, we conducted a prospective, randomized, double-blind study to compare iv and epidural administration of fentanyl infusions. The goals of this study were to determine whether, at comparable levels of analgesia, 1) the severity of side effects was different between iv and epidural administration; and 2) plasma fentanyl concentration differed between the two groups.

Methods

This project was approved by the institutional review board and written informed consent was obtained from each subject. Twenty-eight ASA physical status 2 English-speaking women over the age of 18 with no known opioid tolerance, scheduled to undergo elective cesarean section in the morning, consented to participate. Patients were randomized into two groups, iv or epidural. Those in the iv group received fentanyl intravenously and saline epidurally; the epidural patients received fentanyl epidurally and saline intravenously. Volumes and appearances of both infusions were identical. Patients, nurses, anesthesiologists, and investigators were blinded to the route of administration.

Each patient's postpartum weight was estimated as 4.5 kg less than her prepartum weight, except in the case of one woman with polyhydramnios, whose weight was estimated to be 10 kg less. These estimated postpartum weights, rounded to the nearest 10 kg, were used to determine the rate of delivery of fentanyl. The concentration of solutions varied from 3.8-7.5 $\mu\text{g}/\text{ml}$, depending on the patients' estimated postpartum weight, to deliver 0.75 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ at a rate of 10 ml/h. Solutions were prepared by an individual not involved in the study or patient care.

On the morning of surgery an iv catheter in a forearm and an epidural catheter at the second lumbar interspace were placed. After an epidural test dose of 3 ml of 1.5% lidocaine with epinephrine 1:200,000, 2% lidocaine with

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epinephrine 1:400,000 was administered incrementally until an anesthetic level was demonstrated at thoracic dermatome 4 or higher. If the patient complained of pain during the surgery, more lidocaine was administered epidurally; if discomfort still persisted, 10-mg increments of ketamine were given intravenously.

Immediately after delivery of the infant, each patient received a bolus of fentanyl $1.5 \mu\text{g}/\text{kg}$ either intravenously or epidurally, and a fentanyl infusion at $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (10 ml/h) was begun *via* the same route. Concurrently, a saline bolus and infusion were given *via* the alternative route. Patients were encouraged to call the principal investigator whenever they felt pain, at which time a bolus of fentanyl $0.75 \mu\text{g}/\text{kg}$ (10 ml) was given either intravenously or epidurally in a blinded fashion, depending on the predetermined route of administration, and the infusion rate was increased by $0.375 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (5 ml/h). At the same time an equal volume of saline was given as a bolus *via* the alternate route and the infusion rate of saline was increased proportionately. This adjustment continued over a period of hours until either the patient was comfortable and declined further increases in medication; was so somnolent that she fell asleep during evaluation; or requested more analgesia despite having reached a maximum infusion rate of $2.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (30 ml/h), at which point she was dropped from the study and received intramuscular narcotics. If any patient's pain was controlled, but the side effects were excessive, the infusion rate was decreased by $0.375 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (5 ml/h) if she desired.

Evaluation for respiratory depression was made by measurement of end-tidal P_{CO_2} (ET_{CO_2}) at 1, 2, 4, 6, 8, 10, 12, and 24 h after the beginning of the fentanyl infusion. Patients used soft nose clips and sealed their lips around a mouth piece attached to a low-resistance Hans-Rudolph valve in a T piece. Expired gas was collected through 1-mm tubing connected to a Puritan Bennett Datex 223 carbon dioxide analyzer. This machine was calibrated at least twice daily with room air and 5% CO_2 . All of these measurements were made on patients who had been resting in bed for at least 10 min with the head elevated 30–45 degrees, unless they still had a full sympathetic block immediately after surgery, in which case measurements were made in the supine position. Patients were instructed to breathe quietly and as normally as possible during the data collection, and ET_{CO_2} was measured after at least 1 min of regular breathing. Respiratory rates were noted hourly, either by the principal investigator or by the nurse caring for the patient.

Patients rated their pain, nausea, and pruritus on 100-mm unmarked linear visual analog scales (VAS), anchored with 0 = none, and 100 = worst imaginable, at 1, 2, 4, 6, 8, 10, 12, and 24 h. At the same time their sedation was evaluated independently by the principal investigator

on a scale of 0–3: 0 = alert, awake; 1 = dozing; 2 = asleep, easily aroused; and 3 = asleep, aroused with difficulty. Urinary retention was not evaluated because all patients had indwelling urinary catheters for the duration of the study. The investigator asked a set of standardized questions: "How comfortable are you? Is anything bothering you? Would you like any more pain medicine? Would you like less pain medicine?" The investigator also noted whether any doses of prochlorperazine 5–10 mg im for nausea or diphenhydramine 25–50 mg im for pruritis, written as standing orders, had been administered. Patients were allowed to receive no other sedatives or antiemetics. At the end of the study patients were asked to rate their impression of their pain control on a scale of 1–4: 1 = very satisfactory; 2 = satisfactory; 3 = unsatisfactory; and 4 = very unsatisfactory.

Plasma concentrations of fentanyl were measured at 12 and 24 h at least 1 h after the final adjustment of fentanyl infusion rates were made. Blood for these measurements was drawn from the arm contralateral to the iv infusion and immediately heparinized and centrifuged. The plasma was pipetted off and frozen at -20°C until analyzed by radioimmunoassay by the Bioanalytical Laboratory of Janssen Pharmaceutica in New Jersey. The lowest detection limit for the assay is 0.1 ng/ml and results are reproducible within 10% for the range studied.

Data were analyzed by unpaired two-tail *t* tests. Applying the Bonferroni correction, a *P* value of 0.0125 was considered to be significant for the four variables which evaluated side effects of therapy; a *P* value of 0.025 was considered significant for each plasma fentanyl concentration.

Results

There were 12 patients assigned to the iv group and 16 to the epidural group. There were no significant differences between the two groups prior to beginning the fentanyl infusions (table 1.)

Two patients in the epidural group required intraoperative supplementation of their epidural anesthesia

TABLE 1. Patient Group Characteristics

Characteristic	IV		Epidural	
	Mean	SD	Mean	SD
Age (yr)	30	5	31	5
Height (cm)	162	6	162	6
Preoperative weight (kg)	82	14	81	16
Estimated postpartum weight (kg)	77	12	74	13
Gravity	2.9	0.8	3.4	1.5
Parity	1.2	0.6	1.9	1.1
Preoperative ET_{CO_2} (mmHg)	28	2	28	2
2% lidocaine with epinephrine 1:400,000 (ml)	26	5	23	5
Thoracic anesthetic level	3.2	0.9	2.9	1.6

with iv ketamine (40 and 10 mg). One of these patients also received glycopyrrylate 0.2 mg for nausea and the other midazolam 2 mg for dysphoria. Both patients later had good analgesia with fentanyl infusions. No other patient received any other anesthetic, antiemetic, or sedative medications intraoperatively other than lidocaine and epinephrine used for anesthesia, or fentanyl given intravenously or epidurally as the study drug.

Three patients, all in the iv group, were dropped from the study at 4, 7, and 9 h because of inadequate pain relief despite receiving the maximum allowable infusion rate of $2.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (30 ml/h). This was statistically significant compared with the epidural group ($P = 0.016$). The data from these patients were eliminated from further statistical analysis. All other patients were comfortable after adjusting the infusion rates to between 0.75 and $2.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (10 and 30 ml/h), which was accomplished in all subjects by 12 h after beginning the infusion. Patients were titrated to their requested level of analgesia except for three in the iv group and two in the epidural group who requested "more pain medicine" while falling asleep during the conversation. These five patients meet our criteria for excessive somnolence and were denied increases in their fentanyl infusion rates. No patient ever requested that the infusion rate be decreased. The remaining nine patients in the iv group required $1.88 \pm 0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (25 ± 5.3 ml/h), while the sixteen epidural patients required $1.50 \pm 0.46 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (20 ± 6.1 ml/h; $P = 0.08$). (All values are reported as mean \pm SD.) Intravenous pain scores were 20 ± 16 at 12 h and 14 ± 14 at 24 h. Epidural pain scores were 10 ± 16 at 12 h and 8 ± 13 at 24 h. These were not statistically different between groups ($P = 0.18$ at 12 h and $P = 0.28$ at 24 h).

There were no significant differences between the two groups in the maximum levels of side effects evaluated (table 2). The mean highest ETCO_2 was 33 ± 2.5 for both groups ($P = 0.97$). No patient had a respiratory rate below 12. The highest nausea scores were 12 ± 18 for the iv and 17 ± 25 for the epidural patients ($P = 0.57$). Two patients in the epidural group received prochlorperazine. One of these had received methergine for uterine atony, which led to nausea, vomiting, and persistent painful cramps. Her pain scores were 54 at 12 h and 53 at 24 h. Her highest nausea score was 69.

The highest pruritus scores were 51 ± 31 for the iv and 43 ± 26 for the epidural patients ($P = 0.50$). Sixteen percent of the iv patients and 38% of the epidural patients received diphenhydramine. One epidural patient had such persistent itching after 5 h of fentanyl infusion despite receiving diphenhydramine 50 mg im \times 3 and 25 mg iv \times 1, that she required naloxone 120 μg iv before she was comfortable. The infusion of fentanyl was continued at the same rate per patient request and the 12-h pain score

TABLE 2. Results

	IV		Epidural	
	Mean	SD	Mean	SD
Infusion fentanyl ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$)	1.88	0.4	1.52	0.46
Pain score 12 h	20	16	10	16
Pain score 24 h	14	14	8	13
Highest nausea score	12	18	17	25
Highest pruritus score	51	31	42	26
Highest sedation score	1.8	0.7	1.5	0.5
Highest ETCO_2 (mmHg)	32	2.4	33	2.6
Plasma fentanyl ng/ml 12 h	1.16*	0.27	0.78*	0.23
Plasma fentanyl ng/ml 24 h	1.19	0.21	0.93	0.29

* = $P < 0.025$.

and plasma drug level were evaluated 7 h later. Her severe pruritus did not return.

The highest sedation levels reported by an observer, the principal investigator, were 1.8 ± 0.67 for the iv and 1.5 ± 0.5 for the epidural group ($P = 0.26$). One patient's infant became cyanotic after nursing and was temporarily apneic. The infant was taken immediately to the nursery where he received oxygen by mask and tactile stimulation. Later that afternoon he was again noted to be cyanotic. An evaluation for sepsis showed no evidence of infection. Long-term followup of the infant, including respiratory impedance plethysmography and at-home monitoring, revealed no abnormalities.

The plasma concentrations of fentanyl at 12 h were 1.16 ± 0.27 ng/ml for the iv and 0.78 ± 0.23 ng/ml for the epidural patients. This was statistically significant ($P = 0.001$). By the end of 24 h, the plasma concentrations were 1.19 ± 0.20 ng/ml and 0.93 ± 0.29 ng/ml, respectively. This was not significant ($P = 0.05$). The three subjects who were dropped from the study because of inadequate pain relief had fentanyl concentrations of 1.77, 1.70, and 1.43 ng/ml at 4, 7, and 9 h, respectively.

Patient satisfaction with their pain control, evaluated at the end of 24 h, was similar for both groups. Patients in the iv group rated their pain control method as 1.3 ± 0.5 and those in the epidural group 1.2 ± 0.4 ($P = 0.4$).

Power analyses were performed to examine the probability of detecting differences between the iv and epidural groups for pain scores, severity of side effects, and the plasma concentrations of fentanyl. The variability of the reported pain, nausea, pruritus, and sedation scores was so great that studying an infinite number of subjects could not have discriminated even a 100% difference between the two groups. In contrast, the difference between the iv and epidural plasma fentanyl concentrations at 24 h would have reached statistical significance if an additional seven subjects had been studied with the same variability and difference between the means.

Discussion

Our intention when designing this study was to provide equivalent analgesia in two groups of patients who had undergone a standard operation in order to compare side effects and plasma fentanyl concentrations. Using our stated criteria to titrate the rate of infusion of fentanyl to the point where each patient was comfortable and requested no further increase, three patients in the iv group failed to achieve acceptable analgesia despite infusion rates of $2.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. This corresponded to 30 ml/h. We were reluctant to infuse solution at a faster rate than this into the epidural space. An alternative would have been to unblind the investigator for those patients and to continue to increase the rate of iv infusion. The institutional review board would not allow higher infusion rates for these patients, so this was not possible.

By eliminating those three patients from statistical analysis, we may have biased the results in favor of similar infusion rates for the two groups. However, it was not anticipated that the two groups would require the same rate of infusion of fentanyl. The nine patients remaining in the iv group did have equivalent analgesia to those in the epidural group and are therefore comparable for our stated purposes: to compare the severity of side effects and plasma drug concentrations between the two groups.

Power analyses revealed that, even had an infinite number of subjects been studied, the variability in pain, nausea, pruritus, and sedation scores is so great that it would not have been possible to detect a statistically significant difference between the two groups. Use of the VAS was chosen to evaluate pain, nausea and pruritus because the results are reproducible;⁵ the great variability is inherent in subjective evaluations of biological systems. It is important to note that comparing the mean pain score of 20 at 12 h for the iv group to the score of 10 for the epidural group does not show that the iv patients were suffering twice as much; subjects on patient-controlled narcotic infusions titrate themselves to pain scores of 30–40.

It is not surprising that we found no evidence of respiratory depression in our patients, particularly since they presumably still were experiencing the stimulatory effects of progesterone. Lomessy *et al.* found no significant change in arterial P_{CO_2} after 200 μg of epidural fentanyl in surgical patients,⁶ nor did Ahuja and Strunin after a bolus of 1.5 $\mu\text{g}/\text{kg}$ followed by an infusion of 0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 18 h.⁷ Those investigators who have examined the slope of the ventilatory response to CO_2 , a more sensitive test, have found respiratory depression after a bolus of 200 μg given epidurally⁴ and after an epidural bolus of 1 $\mu\text{g}/\text{kg}$ followed by an infusion of 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 18 h,² although neither of these was of evident clinical significance.

The low scores our patients reported for nausea are in accord with other investigations. Naulty *et al.* found nausea in 7% of parturients after cesarean section and epidural fentanyl.⁸ Welchew *et al.* reported nausea in 17% of patients after upper abdominal surgery who received 100 μg of epidural fentanyl and none in those who received 200 μg .⁹ Patients receiving 60 $\mu\text{g}/\text{h}$ after thoracic surgery reported nausea scores of 0.86 out of a possible 10.³

Pruritus was a very frequently reported side effect in patients in both the iv and epidural groups. Other studies have reported the incidence of pruritus to be from 13–36%.^{3,9–11} It has been suggested that parturients may be more susceptible to the pruritic effects of spinal narcotics than the general population.¹¹ Indeed, Naulty *et al.* reported that the incidence of pruritus in patients after cesarean section who received epidural fentanyl was 30%, and 40% (two out of five) in patients who received epidural saline alone.⁸

The mean sedation scores for subjects in our study indicate that most of the time the patients were either dozing or asleep but easily aroused whether they were in the iv or epidural groups. Cohen and Woods found that the duration of time patients spent sleeping after cesarean section was similar in parturients whether they had received epidural morphine or iv morphine.¹²

One other study has compared the incidence and severity of side effects in patients given either epidural and iv fentanyl. Loper *et al.* gave fentanyl 100 $\mu\text{g}/\text{h}$ either epidurally or intravenously to 20 patients after anterior cruciate ligament repair.¹³ Their two groups of patients were comparable in reported VAS pain scores. There was no statistically significant difference between the incidence of symptoms or treatment for nausea, pruritus, or urinary retention. These investigators concluded that continuous epidural infusion offers no advantage over continuous iv infusion at the same dose.

The episode involving the apneic infant is of unknown significance. The neonate's mother was receiving epidural fentanyl at 1.125 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (15 ml/h), one of the lowest infusion rates in our study. The mother's plasma concentration of fentanyl was 0.53 ng/ml at 12 h, and 0.68 ng/ml at 24 h, also some of the lowest among our patients. The gastric absorption of fentanyl in rats is only 1.5%;¹⁴ however, 51% of sublingually administered fentanyl is absorbed after 10 min in adult humans.¹⁵ Fentanyl, being more lipophilic, may be more easily excreted into breast milk than some other narcotics such as morphine. It is unknown how much fentanyl is excreted in breast milk after prolonged infusion; none was detected in colostrum 1 h after the epidural administration of a bolus of 100 μg fentanyl after cesarean section.¹⁶ As no plasma concentration of fentanyl was drawn from the apneic infant nor naloxone administered, it is not clear whether the apnea

was due to a narcotic effect. It may have been an infant who was particularly sensitive to respiratory depressants, but this seems unlikely in light of the normal long-term evaluations. Obviously, if a fentanyl infusion provides excellent maternal analgesia, but endangers nursing infants, another method of relieving pain must be used. Further investigation is necessary.

The iv infusion rate of $1.88 \pm 0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ needed to achieve good analgesia in our patients is reasonably similar to rates reported by others.^{1,17,18} The epidural infusion rate we report is higher than has been reported by most other investigators;^{7,13,19} however, some of them did not use VAS pain scores and instead relied on observers' assessments of pain. It may be that our study design kept patients at higher infusion rates than they needed. Another possibility is that our patient population differed in health, age, and expectation of pain relief than others. Some patients confessed that they desired the sedative effect of the higher infusion rates in order to enable them to sleep more while in the hospital.

Reported plasma fentanyl concentrations after epidural infusion have varied widely, from undetectable to 4.7 ng/ml.^{2,3,7,20,21} Some reported concentrations are greater than the 2–3.2 ng/ml reported to be needed for sufficient analgesia with systemic medication.²²

In our study, there was a significant difference in plasma fentanyl concentrations at 12 h between the two groups of patients. This may have been due to nonspecific binding of epidurally administered fentanyl to sites in the epidural or paravertebral spaces, delaying access of the drug to the intravascular compartment. It is not unreasonable to expect that after 24 h of infusion, equilibrium may have been nearly achieved, explaining why the difference in plasma concentrations is less after long-term administration.

The significant difference in plasma concentrations at 12 h between the iv and epidural patients experiencing comparable analgesia suggests, but does not prove, that epidural fentanyl functions at the spinal cord level. This had been proposed earlier by observations which demonstrated that the duration of action of epidural fentanyl is longer than that of iv fentanyl.^{8,23} However, because the plasma concentration associated with epidural administration can approach or exceed that seen after im or iv injection,^{1–4} it is not clear whether there is a redistribution of the drug to receptors in the brain, spinal cord, or other parts of the nervous system. Plasma fentanyl concentrations may be easily assayed but clinically irrelevant, as they may not reflect the degree of binding to narcotic receptors in drug-effect compartments such as the spinal cord and brain. The demonstration in this study of similarity in the severity of side effects suggests that many of the actions of fentanyl are not specific to the spinal cord or to the brain, but that the drug acts at more than one

location, irrespective of the location of its injection into the body.

In conclusion, we found that fentanyl produces effective analgesia of comparable quality when infused either intravenously or epidurally. Despite lower plasma concentrations of fentanyl after 12 h of infusion in the patients who received epidural fentanyl, the severity of nausea, pruritis and sedation, and end-tidal P_{CO_2} is similar in both groups. Thus there appears to be no clinical advantage to epidural infusion over iv infusion of fentanyl for analgesia after cesarean section.

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