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Bupivacaine 0.01% and/or Epinephrine 0.5 μg/ml Improve Epidural Fentanyl Analgesia after Cesarean Section

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Background: **The authors studied the addition of bupivacaine and epinephrine, separately and together, to epidural fentanyl to determine whether this improved postcesarean analgesia and reduced the incidence of side effects.**

Methods: **After elective cesarean section, 100 parturient patients who received fentanyl (3 μg/ml) epidurally for 48 h were allocated randomly in a double-blinded manner to four groups to receive, in addition to the study solution, 0.01% bupivacaine, 0.5 μg/ml epinephrine, both, or neither. A neurologic assessment of breast-fed neonates was made at 2 and 48 h of life. Plasma fentanyl concentrations were determined in a subset of patients at intervals after treatment.**

Results: **Patients receiving fentanyl alone made more attempts at patient-controlled analgesia ($P < 0.01$), required a greater total dose of fentanyl ($P < 0.01$), reported more pain ($P < 0.003$) and less satisfaction ($P < 0.003$), and had more nausea and urinary retention ($P < 0.05$) than all other groups. Patients who received bupivacaine with or without epinephrine had better overall satisfaction scores than those who did not receive bupivacaine ($P < 0.001$), and they required less fentanyl ($P < 0.02$) than patients who received fentanyl with only epinephrine. Motor blockade or orthostatic hypotension did not develop in any patient, and all patients could ambulate without difficulty. Neurobehavioral scores, which were similar among all neonates, were within the normal range. Plasma concentrations of fentanyl increased after epinephrine-containing solutions were discontinued.**

Conclusions: **During the conditions of this study, the addition of epinephrine and bupivacaine to a 3-μg/ml epidural fentanyl solution for postcesarean section pain relief provided superior analgesia compared with fentanyl alone or fentanyl with epinephrine. Whether increasing the concentration of fentanyl alone might improve the efficacy of fentanyl remains unclear. (Key words: Analgesia; fentanyl plasma concentration; neonatal neurologic assessment; obstetric; postepidural infusion; postoperative analgesia.)**

THERE have been conflicting reports as to whether the addition of bupivacaine or epinephrine, or both, to epidural fentanyl improves postoperative analgesia.[1–5] The source of these conflicts may lie in variations among the studies in experimental protocols. When a high concentration of opioid was used, the addition of bupivacaine did not enhance the already satisfactory analgesic effect of the opioid.[3,4,6] The primary objective of the current study was to determine the effect on the quality of analgesia and opioid-induced side effects of the addition of either very-low-dose bupivacaine or epinephrine, or both, to epidural fentanyl in patients after cesarean section delivery. We used an infusion volume that we found in our clinical practice to be optimal and a concentration of fentanyl that we estimated would provide adequate but improvable analgesia. Secondary objectives were to determine whether these epidural solutions adversely affect the neurobehavioral scores of breast-fed neonates and to confirm our previous observations[1,7] of an increase in the plasma concentration of opioid after an epinephrine-containing solution was discontinued.

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Materials and Methods

The study was approved by the Institutional Review Board of the New York Hospital Medical Center of Queens, and written informed consent was obtained from each patient. We studied 100 parturient patients at full term who were classified as American Society of Anesthesiologists physical status 1 or 2 and scheduled to undergo elective cesarean delivery during epidural anesthesia. We excluded patients with a history of known dependence on opioids, allergy to local anesthetics, or accidental dural puncture.

After the patients received 30 ml sodium citrate, 0.3 M, orally, a transdermal scopolamine patch, and an intravenous infusion of 1.5 to 2 l of lactated Ringer's solution, lumbar epidural anesthesia to achieve a T4-6 sensory level was established by injecting 3 ml lidocaine, 1.5%, with 5 μg/ml epinephrine, followed by 18–20 ml lidocaine, 2%, and 5 μg/ml epinephrine *via* a catheter placed at the L3-4 interspace. The catheter was directed cephalad 3 cm into the epidural space. A urethral catheter was placed for all patients. During surgery, the patients were maintained supine with left uterine displacement and were monitored continuously using an automated blood pressure cuff, electrocardiography, and pulse oximetry. Oxygen was supplied by face mask at 6 l/min until delivery. No opioids were administered before the neonates were delivered. After delivery, 0.02 units/ml oxytocin was infused for 6–8 h to reduce blood loss and prevent subinvolution of the uterus and the spread of endometritis.

After delivery, patients were allocated randomly in a double-blinded manner to one of four equal groups according to a table of random numbers. Group F received 3 μg/ml fentanyl diluted in saline. Group FB received 3 μg/ml fentanyl with 0.01% bupivacaine in saline. Group FE received 3 μg/ml fentanyl with 0.5 μg/ml epinephrine in saline. Group FBE received 3 μg/ml fentanyl with 0.01% bupivacaine and 0.5 μg/ml epinephrine in saline. A study physician prepared and placed the solutions in 1,000-ml coded bags. Neither the investigator involved in the management and assessment of the patient nor the patient was aware of the solution being administered. Immediately after delivery of the neonate, the epidural catheter was connected to a portable Abbott Pain Management Provider (Abbott Laboratories, North Chicago, IL). Each patient received an initial epidural infusion of 16 ml/h and was allowed self-administered patient-controlled analgesia (PCA) boluses of 3 ml with a 10-min lockout time; six boluses were allowed in 1 h. Treatment lasted 48 h. Every 4 h, or sooner if requested, an investigator evaluated the patient for side effects, complications, and quality of analgesia. If patients were sleeping, they were not disturbed. To provide satisfactory analgesia, the investigator increased or decreased the infusion rate by 2 ml/h and administered additional 3- to 6-ml boluses if needed to achieve a pain score less than 3. Lockout times and the amount of self-administered PCA bolus doses were not changed throughout the treatment. The decision to decrease the infusion rate was made jointly by the patient and the investigator based on the number of PCA requests made during the preceding 4-h interval and the patient's assessment of whether she would tolerate a small decrease in the infusion rate. If no additional rescues were needed in the previous 4 h, the investigator offered to reduce the infusion rate by 2 ml/h. If the patient refused, the infusion rate was not reduced. Pain intensity at rest was assessed using a 10-point linear visual analog scale (0 = no pain, 10 = most severe pain). The patients were assessed for the incidence of any pruritus, facial pruritus (as indication of rostral opioid spread), sedation, nausea, vomiting, backache, urinary retention, and uncomfortable uterine cramping. The severity of these side effects was assessed using a three-point scale (1 = mild, 2 = moderate, and 3 = severe). At the patient's request, severe pruritus or severe sedation were treated by administering 0.04-mg increments of intravenous naloxone until relief was achieved, whereas nausea and vomiting were treated by administering a 10-mg intravenous dose of metoclopramide. Urinary retention after removal of the urethral catheter was treated by repeated straight catheterization. The incidence of side effects indicates the number of patients in whom the side effect occurred, regardless of the duration or the number of time intervals when it occurred. Motor block was assessed using a score modified from that described by Bromage[8] (1 = complete block, unable to move feet or knees; 6 = able to perform partial knee bend while standing).

Patients received no additional systemic opioids or sedatives during treatment. Patients had intravenous access throughout, and blood pressure, pulse, respiratory rate, and adequacy of respiration were monitored every 1 or 2 h by a nurse during the treatment. An investigator evaluated side effects and respiratory rate every 30 min for 6 h after the infusion was discontinued. At the start of the study, urethral catheters were kept in place for 24 h. Later, the obstetricians changed the policy and decided that it was safe to remove the urethral catheters 12 h after surgery. Twelve to 24 h after surgery, during the

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Table 1. Patient Demographic Characteristics

Characteristic	Group F	Group FB	Group FE	Group FBE
Age (yr)	28.8 ± 5.2	29.6 ± 4.5	30.4 ± 4.3	30.2 ± 3.8
Weight (kg)	77.4 ± 11.4	81.8 ± 15.7	76.5 ± 13.2	82.7 ± 12.5
Height (cm)	157.9 ± 6.1	156.9 ± 4.5	159.3 ± 6.8	157.2 ± 4.5
Parity	1 (0–2)	0 (0–3)	1 (0–2)	1 (0–2)

Values for age, weight, and height are mean ± SD for 25 patients in each group; parity is expressed as median (range). There were no significant differences among groups (ANOVA).

F = 3 μg/ml fentanyl; FB = 3 μg/ml fentanyl + 0.01% bupivacaine; FE = 3 μg/ml fentanyl + 0.5 μg/ml epinephrine; FBE = 3 μg/ml fentanyl + 0.01% bupivacaine 0.5 μg/ml epinephrine.

daytime, if patients showed normal leg strength (modified Bromage score of 5), an attempt was made to let them walk. Heart rate and blood pressure were measured by nurses before and 2 min after the start of each ambulation to assess the presence of orthostatic hypotension (defined as a decrease in systolic blood pressure > 20% from baseline) and bradycardia (defined as a heart rate < 60 beats/min). Patients were questioned about the presence of dizziness, nausea, or vomiting. Nurses were instructed not to allow any patient to walk who had evidence of hypotension, bradycardia, dizziness, or lower extremity weakness (modified Bromage score < 5). Overall satisfaction with treatment was assessed at the discontinuation of treatment using a 10-point visual analog scale (0 = no satisfaction, 10 = best satisfaction). Breast-fed neonates were assessed at 2 and 48 h of life by a pediatrician blinded to the solution administered using the Neurologic and Adaptive Capacity Score.[9]

From eight or nine patients selected arbitrarily from each group, venous blood samples were drawn from an antecubital vein of the arm contralateral to the one with an intravenous line 2 h before, at, and 0.5, 1, 1.5, 2, and 4 h after discontinuation of the epidural. After the samples were centrifuged, plasma was stored at −20°C until analysis. Plasma concentrations of fentanyl were determined using a modified[10] radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). The fentanyl assay has a limit of detection of 0.1 ng/ml and intra- and interassay coefficients of variation of 4.1% and 5.7%, respectively.

Statistical Analysis

Data are presented as the mean ± SD unless otherwise indicated. Data measured progressively were analyzed by repeated measures analysis of variance (ANOVA), and overall differences between groups were assessed with contrasts using StatView, SuperAnova (Abacus Concepts, Berkley, CA). Data expressed as averages or sums of all values obtained during the 48 h of the study were analyzed by ANOVA, with a Bonferroni/Dunn *post hoc* test applied for comparisons of four groups and by Student's unpaired *t* test when two groups were compared. The incidence of side effects was analyzed using Fisher's exact or chi-squared tests as appropriate. A probability value < 0.05 was considered significant.

Results

Groups did not differ in age, weight, height, or parity (table 1). Ninety-two patients completed the entire study. The epidural treatment was discontinued in five patients because of inadequate pain control (four in group F and one in group FE) and in three patients because of a dislodged epidural catheter (one each in groups F, FE and FBE). At 24 h there were 22, 25, 23, and 24 patients in groups F, FB, FE, FBE, respectively, and at 48 h there were 20, 25, 23, and 24 patients in the respective groups.

The mean infusion rate during successive 4-h intervals of the 48 h of the study was greater among patients in group F (repeated measures ANOVA, $P < 0.001$) than among patients in the other three groups and was greater among patients in group FE than among those in group FBE (repeated measures ANOVA, $P < 0.001$; fig. 1). The mean of the infusion rates averaged for each patient during the course of the study, the mean total number of PCA attempts, the mean volume administered as boluses, and the mean total volume administered

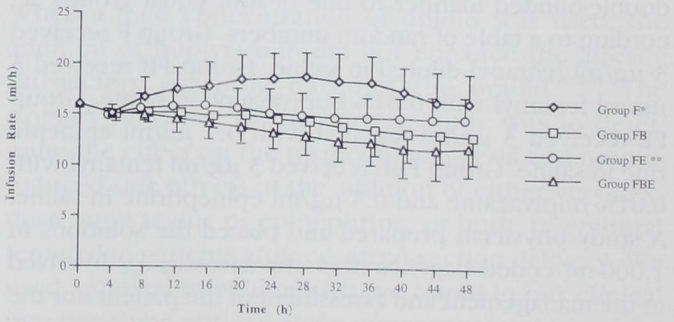

Fig. 1. Epidural infusion rate at 4-h intervals during epidural treatment. Values are the mean ± SD for all patients remaining at the indicated time. Plot symbols for groups FB and FE are slightly offset for clarity. F = 3 μg/ml fentanyl, FB = 3 μg/ml fentanyl + 0.01% bupivacaine, FE = 3 μg/ml fentanyl + 0.5 μg/ml epinephrine, FBE = 3 μg/ml fentanyl + 0.01% bupivacaine + 0.5 μg/ml epinephrine. *Significantly greater than groups FB, FE, FBE (by repeated measures of analysis of variance [ANOVA], $P < 0.001$). **Significantly greater than group FBE (by repeated measures of ANOVA, $P < 0.001$).

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Table 2. Epidural Infusion Characteristics

	Group F (n = 21)	Group FB (n = 25)	Group FE (n = 23)	Group FBE (n = 23)
Mean total dose 0–48 h (ml/h)	17.4 ± 1.8	14.3 ± 1.5*	15.1 ± 1.5*	13.4 ± 1.4*,†
Total PCA attempts 0–48 h (n)	73.9 ± 34.2	29.4 ± 24.3*	40.4 ± 29.1*	16.6 ± 10.9*†
Total volume as boluses (ml)	151.2 ± 86.3	72.8 ± 63.2*	89.4 ± 52.1*	49.0 ± 58.9*
Total volume administered (ml)	1005 ± 134	745 ± 105*	822 ± 115*	688 ± 119*†

Values are mean ± SD.

F = 3 μg/ml fentanyl; FB = 3 μg/ml fentanyl + 0.01% bupivacaine; FE = 3 μg/ml fentanyl + 0.5 μg/ml epinephrine; FBE = 3 μg/ml fentanyl + 0.01% bupivacaine + 0.5 μg/ml epinephrine.

* Significantly different from group F, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.01$.

† Significantly different from group FE, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.01$.

were all greater for the group receiving fentanyl alone than for the other three groups (ANOVA, $P < 0.01$; table 2). In addition, mean infusion rate, total PCA attempts, and total volume administered to patients in group FE were greater than in those in group FBE (ANOVA, $P < 0.01$; table 2). The number of patients who refused to allow the investigator to reduce the basal rate when requested during treatment was 10 of 20 (50%), 10 of 25 (40%), 15 of 23 (65%), and 8 of 24 (33%) for groups F, FB, FE, and FBE, respectively.

Patients in group F required a greater total dose of fentanyl, both during the first 24 h and during the entire 48 h of the study, than did patients in the other three groups (ANOVA, $P < 0.01$; table 3). Those patients in group FE required more fentanyl than did those in group FBE (ANOVA, $P < 0.03$; table 3). The total dose of bupivacaine received at 24 and 48 h was significantly less among patients in group FBE than in those in group FB (Student's unpaired t test, $P < 0.02$; table 3).

Group F patients reported higher mean pain scores than did patients in the other three groups, and group FE patients had higher scores than did those in groups FB and FBE (repeated measures ANOVA, $P < 0.01$; fig. 2). As summarized in table 4, patients who received fentanyl alone had significantly higher average pain scores and lower satisfaction scores than did all other groups. Patients in groups FBE and FB reported greater overall satisfaction than did those in group FE. Pain scores and overall satisfaction were similar among patients in groups FB and FBE (table 4).

Table 5 shows the incidence of side effects and complications. Clinically significant motor block (modified Bromage score < 6), hypotension at rest, or orthostatic hypotension did not develop in any patient. There were no significant differences among the groups with respect to the duration of urethral catheterization, which was 18.1 ± 4.2 h, 19.0 ± 4 h, 17.9 ± 5 h, and 18.4 ± 4 h for groups F, FB, FE, FBE, respectively. When the hourly infusion rate increased to more than 18 ml/h, many patients were reluctant to request a further increase in the infusion rate because this caused back pain and because they did not believe that further rate increases would improve analgesia. There were 34 reports of back pain rated as severe, of which 33 occurred in group F. All

Table 3. Mean Total Dose of Fentanyl and Bupivacaine Received by Patients at 24 and 48 Hours of Treatment

	Group F	Group FB	Group FE	Group FBE
Fentanyl 24 h (μg)	1,557 ± 248	1,209 ± 126*	1,271 ± 207*	1,081 ± 224*†
Fentanyl 48 h (μg)	2,944 ± 378	2,245 ± 290*	2,380 ± 407*	2,050 ± 265*†
Bupivacaine 24 h (mg)	N/A	40.3 ± 4.2	N/A	36.0 ± 7.5‡
Bupivacaine 48 h (mg)	N/A	74.8 ± 9.6	N/A	67.9 ± 8.9‡

Values are mean ± SD for all subjects remaining in the study at the end of the time period.

N/A = not applicable.

* Significantly different from group F, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.01$.

† Significantly different from group FE, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.03$.

‡ Significantly different from group FB, Student's unpaired t test, $P < 0.02$.

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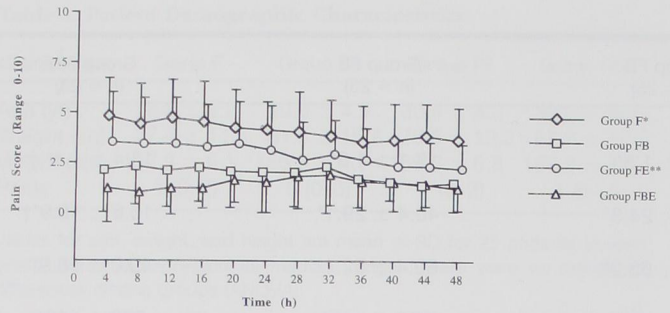

Fig. 2. Pain scores at 4-h intervals during epidural treatment. Values are the mean ± SD for all patients remaining at the indicated time. Plot symbols for groups FB and FE are slightly offset for clarity. Pain scale: 0 = no pain, 10 = worst pain ever. F = 3 μg/ml fentanyl, FB = 3 μg/ml fentanyl + 0.01% bupivacaine, FE = 3 μg/ml fentanyl + 0.5 μg/ml epinephrine; FBE = 3 μg/ml fentanyl + 0.01% bupivacaine + 0.5 μg/ml epinephrine. *Significantly greater than groups FB, FE, FBE (by repeated measures of analysis of variance [ANOVA], $P < 0.01$). **Significantly greater than groups FB and FBE (by repeated measures of ANOVA, $P < 0.01$).

but four episodes were associated with flow rates of ≥ 18 ml/h. Of the five patients who requested discontinuation from the study because of inadequate pain relief, four (16%, chi-squared analysis, $P < 0.03$) were in group F and one (4%, not significant) was in group FE. No patient in either group receiving bupivacaine reported inadequate pain relief (table 5).

There were no differences among treatment groups with respect to mean neonatal adaptive or neurologic capacity or combined scores at either 2 or 48 h of life (table 6). The mean hospital stay, which did not differ among the groups, was 4.4 ± 0.1, 4.1 ± 0, 4.3 ± 0.1, and 4.1 ± 0.1 days.

There was no significant change in plasma concentration of fentanyl in any group during the 2 h before the epidural was discontinued. At the time of discontinuation, plasma concentrations of fentanyl were similar in groups F, FB, FE, FBE (0.52 ± 0.15, 0.43 ± 0.11, 0.56 ± 0.29, and 0.41 ± 0.20 ng/ml, respectively). After the epidural was discontinued, the mean concentration of fentanyl gradually decreased from baseline in groups F and FB (fig. 3A). However, in groups FE and FBE, the mean concentration increased from the time of discontinuation to 1 h after discontinuation before it decreased. This increase averaged 34% (repeated measures ANOVA, $P < 0.01$) in group FE and 20% (not significant) in group FBE. After discontinuation of the infusion, plasma concentrations of fentanyl were higher in group FE than in groups FB or FBE (repeated measures ANOVA, $P < 0.04$; fig. 3A). The highest plasma concentrations observed, 1.0, 1.1, and 1.2 ng/ml, occurred in three patients in the FE group. Repeated measures of ANOVA showed a significant interaction ($P < 0.03$) between time and group, with only those patients who were receiving epinephrine showing an increase in plasma concentration of fentanyl after discontinuation (fig. 3A). Grouping the patients into those who had and those who had not received epinephrine also showed a significant difference between groups progressively (repeated measures ANOVA, $P < 0.001$; fig. 3B), with fentanyl gradually decreasing in the group that had not received epinephrine and increasing by 32% 1 h after the epidural was discontinued in the epinephrine-receiving group before beginning to decrease. No patient in any group experienced light-headedness or decreased respiratory rate in association with the increased plasma concentration of fentanyl.

Discussion

This study shows that adding bupivacaine and epinephrine to a 3-μg/ml fentanyl solution provides superior analgesia with fewer side effects and no lower-extremity weakness or orthostatic hypotension when compared with the fentanyl alone. Whether increasing the concentration of fentanyl alone might improve the efficacy of fentanyl remains unclear. We anticipated that 3 μg/ml fentanyl administered at an initial infusion rate of 16 ml/h and augmented by patient- or investigator-administered boluses would provide analgesia that was sufficient to satisfy patients while still permitting us to determine whether adding bupivacaine, epinephrine, or

Table 4. Cumulative Pain and Overall Satisfaction Scores

	Group F	Group FB	Group FE	Group FBE
Mean pain score (0–48 h)	4.1 ± 1.4	2.0 ± 1.1*	2.9 ± 1.4*	1.4 ± 0.9*†
Overall satisfaction score	5.0 ± 1.0	8.5 ± 0.8*†	6.3 ± 1.1*	8.8 ± 0.5*†

Values are mean ± SD for 25 patients in each group. Pain scale: 0 = no pain; 10 = worst pain ever. Satisfaction scale: 0 = no satisfaction; 10 = best satisfaction.

* Significantly different from group F, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.003$.

† Significantly different from group FE, ANOVA with Bonferroni/Dunn post hoc test, $P < 0.001$.

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Table 5. Incidence of Side Effects and Complications

	Group F	Group FB	Group FE	Group FBE
Pruritus	21 (84)	21 (84)	22 (88)	19 (76)
Facial pruritus	8 (32)	7 (28)	6 (24)	2 (8)
Pruritus requiring treatment	17 (68)*	6 (24)	13 (52)*	4 (16)
Sedation	20 (80)	20 (80)	21 (84)	17 (68)
Nausea	8 (32)*	1 (4)	4 (16)	0 (0)
Vomiting	5 (20)	1 (4)	3 (12)	0 (0)
Backache	21 (84)*	6 (24)	16 (64)*	9 (36)
Cramping score = 3	19 (76)	14 (56)	17 (68)	10 (40)
Urinary retention	9 (36)*	0 (0)	5 (20)	0 (0)
Respiratory rate <12 breaths/min	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuation due to dislodged catheter	1 (4)	0 (0)	1 (4)	1 (4)
Discontinuation due to inadequate pain control	4 (16)*	0 (0)	1 (4)	0 (0)
Difficulty with ambulation (Modified Bromage Score <6)	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension upon ambulation	0 (0)	0 (0)	0 (0)	0 (0)
Bradycardia upon ambulation	0 (0)	0 (0)	0 (0)	0 (0)

Values are number of patients (% of group) in whom side effects occurred at one or more time points.

* Chi square, $P < 0.05$.

both would improve the analgesia without producing additional side effects. However, this dose was barely satisfactory for the fentanyl-only group. The mean pain score of 4.1 ± 1.4 for this group was greater than our target score of ≤ 3, and 16% of patients in this group dropped out of the study. Increasing the infusion rate or adding boluses did not improve patient satisfaction; much to the contrary, greater infusion rates caused patient discomfort because of back pressure, and total doses of fentanyl increased the incidence of opioid-related side effects. Our chosen concentration and infusion rate of fentanyl were more successful in the presence of bupivacaine or epinephrine, or both, to provide optimal analgesia. Although we measured pain scores only at rest, we expect that the differences in the efficacy between treatments would be present not only at rest, but also during cough or mobilization. Our mode of drug administration included continuous infusion of our study solution at an initial rate of 16 ml/h, self-administered PCA boluses of 3 ml, a 10-min lockout time, along with the possibility of an investigator-altered basal rate, and the patient's participation in the decision to alter the basal rate. This mode of drug administration is based on previous clinical experience noting that pain intensity increases when patients cough or walk, and many patients refuse to decrease their infusion rate even though they did not require additional doses at rest.

Although the addition of either low concentration (0.01%) of bupivacaine or, to a lesser extent, 0.5 μg/ml epinephrine to epidural fentanyl produced an improvement in analgesia compared with fentanyl alone, the bupivacaine-containing solutions were associated with greater overall satisfaction than those without bupivacaine. It has been postulated that the interaction between epidural or intrathecal opioids and local anesthetics is synergistic.[11] Although this has not been proved in

Table 6. Neonatal Adaptive, Neurological, and Total Capacity Scores

	Group F (n = 16)	Group FB (n = 21)	Group FE (n = 15)	Group FBE (n = 15)
Adaptive Capacity Score				
2 h of life	8.2 ± 0.9	7.4 ± 1.2	7.8 ± 0.9	7.6 ± 1.0
48 h of life	9.6 ± 0.5	9.6 ± 0.6	9.9 ± 0.4	9.9 ± 0.3
Neurological Capacity Score				
2 h of life	27.0 ± 1.1	27.0 ± 1.9	27.2 ± 1.7	27.6 ± 1.8
48 h of life	29.2 ± 0.6	29.0 ± 0.8	29.2 ± 0.8	28.8 ± 1.0
Total Score				
2 h of life	35.7 ± 1.8	34.0 ± 2.9	34.9 ± 1.9	35.2 ± 2.4
48 h of life	38.8 ± 0.8	38.6 ± 0.9	39.1 ± 0.8	38.6 ± 1.0

Values are mean ± SD for breast-fed neonates. There were no significant differences among the groups in adaptive or neurological capacity or in total scores at either 2 h or 48 h (ANOVA). Maximum possible scores: Adaptive Capacity = 10; Neurological Capacity = 30; Total Score = 40.

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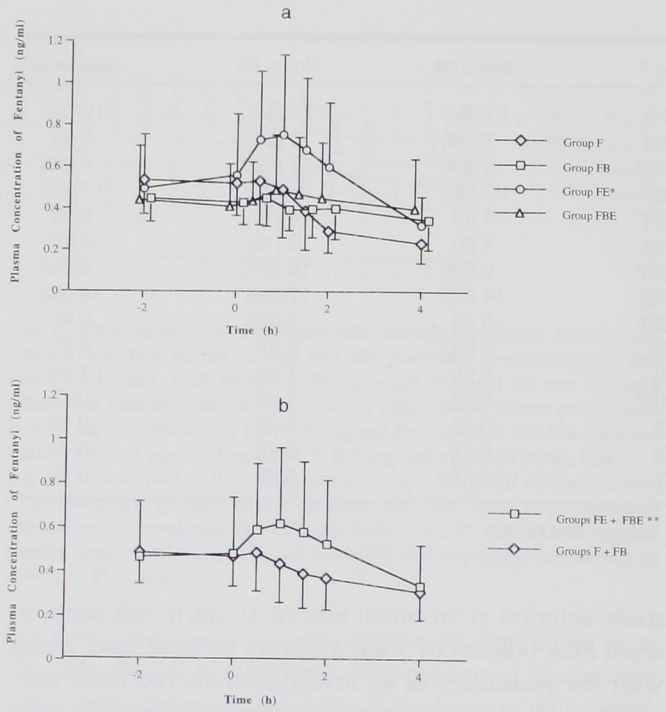

Fig. 3. (*A*) Plasma concentrations of fentanyl in four groups of patients before and after discontinuation of treatment. (*B*) Plasma concentrations of fentanyl after discontinuation of treatment in patients receiving or not receiving epinephrine in the study solution. Values are the mean ± SD. Time 0 is time of discontinuation of treatment. Plot symbols for groups FB and FBE in panel A are slightly offset for clarity. F = 3 μg/ml fentanyl, FB = 3 μg/ml fentanyl + 0.01% bupivacaine, FE = 3 μg/ml fentanyl + 0.5 μg/ml epinephrine; FBE = 3 μg/ml fentanyl + 0.01% bupivacaine + 0.5 μg/ml epinephrine. *Significantly greater than groups FB and FBE (by repeated measures of analysis of variance [ANOVA], $P < 0.04$). **Significantly greater than group F + FB (by repeated measures of ANOVA, $P < 0.001$).

humans, synergistic antinociceptive interactions between opioids and local anesthetics administered intrathecally have been shown in rats.[11,12] However, several studies[3–6,13] report that the addition of 0.1% bupivacaine does not improve epidural opioid analgesia. Most of these studies used a high dose of opioid that was effective by itself in control groups, therefore, any improvement in analgesia from the addition of an adjuvant would have been difficult to show. It appears that the addition of epinephrine to fentanyl–bupivacaine does not improve the quality of treatment or decrease fentanyl-related side effects at the doses that we used, but it decreases bupivacaine requirements. Recently, epidural epinephrine (100 μg) administered to healthy volunteers was shown to have a modest analgesic effect in some, presumably *via* binding of epinephrine to α_2-adrenoreceptors.[14] Although our patients received smaller epinephrine doses than these volunteers, it appears that when added to epidural fentanyl, epinephrine reduced fentanyl requirements to a degree comparable to that of the addition of bupivacaine. An additional explanation for the lack of effect of epinephrine may be its administration at a lumbar level, which is far from the corresponding spinal cord level. This may prevent such low doses of epinephrine from reaching the α_2-receptors in an adequate concentration.

The occurrence of pruritus severe enough to necessitate treatment was less frequent when bupivacaine was added to fentanyl. The incidence of nausea was greatest in the fentanyl-only group, which received the highest dose of fentanyl. These side effects are thought to result from the rostral spread of opioid within the cerebrospinal fluid to the level of the trigeminal nucleus or subnucleus caudalis.[15] We suggest that because the addition of bupivacaine reduced the fentanyl requirement, a lower concentration of fentanyl may have been present at the brainstem, thus reducing side effects. Another explanation is that patients with inadequate analgesia have a higher incidence of nausea and vomiting. The incidence of urinary retention was also greatest in the group that received fentanyl alone and did not occur at all when bupivacaine was added to epidural fentanyl. Despite differences in fentanyl dose requirements among the mothers, breast-fed newborns in the various groups had equally high neurobehavioral scores. To our knowledge, this is the first report of neurobehavioral scores of breast-fed neonates after the use of epidural fentanyl for post-cesarean section analgesia.

In previous studies,[1,7] we reported an increase in the plasma concentration of opioids after termination of prolonged epidural epinephrine-containing opioid study solution that was accompanied by patient reports of dizziness, nausea, and vomiting for as many as 6 h. We speculated that the 250% increase in the plasma concentration of buprenorphine,[7] the 71% increase in the plasma concentration of sufentanil,[1] and the 24% increase in the plasma concentration of fentanyl[1] after discontinuation of epinephrine-containing opioid infusions were the result of increased perfusion of epidural tissues and a washout of stored opioids that accumulated in these tissues during the treatment. The finding that there was a greater increase in plasma concentrations of sufentanil and buprenorphine compared with fentanyl after treatment was probably because of their greater lipid solubility, resulting in greater accumulation in tissues. In the current study, the fentanyl plasma concentration increased an average of 32% after discontinuation

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of epinephrine-containing solutions. However, no patient reported any side effects such as the light-headedness that we found with the more lipid-soluble sufentanil[1] after discontinuation of the epidural treatment. It is intriguing to note that when bupivacaine was added to the epidural fentanyl with epinephrine (group FBE *vs.* FE), the increase in the fentanyl level after discontinuation of epidural treatment was attenuated. We speculate that this occurred because the vasodilating property of bupivacaine counteracted the vasoconstrictive effect of epinephrine. However, another explanation may be that the FBE group, which received less total fentanyl, had less fentanyl accumulated in tissue.

For the conditions of this study, we conclude that patients who received fentanyl alone received the highest dose of fentanyl, were least satisfied with their pain relief, had the highest incidence of nausea and urinary retention, and most frequently requested discontinuation of treatment. The addition of epinephrine or bupivacaine to fentanyl reduced the total volume of study solution and the total fentanyl dose administered in 48 h. The addition of epinephrine to fentanyl improved satisfaction, but not as much as the addition of low-dose bupivacaine. The combination of all three drugs allowed us to decrease the necessary dose of bupivacaine.

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