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Continuous Infusion Epidural Analgesia during Labor: A Randomized, Double-blind Comparison of 0.0625% Bupivacaine/0.0002% Fentanyl Versus *0.125% Bupivacaine*

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The analgesic efficacy of the continuous epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl was compared with the infusion of 0.125% bupivacaine alone in a randomized, double-blind study of nulliparous women. Each patient received, in sequence: 1) 3 ml of 0.5% bupivacaine with 1:200,000 epinephrine; 2) 6 ml of study solution 1 (bupivacaine-fentanyl group: 0.125% bupivacaine/0.0008% fentanyl; bupivacaine-only group: 0.25% bupivacaine alone); and 3) a continuous epidural infusion of study solution 2 at a rate of 12.5 ml/h (bupivacaine-fentanyl group: 0.0625% bupivacaine/0.0002% fentanyl; bupivacaine-only group: 0.125% bupivacaine alone). The epidural infusion was discontinued at full cervical dilatation, but patients who lacked perineal anesthesia received one or two 5-ml boluses of study solution 3 (bupivacaine-fentanyl group: 0.0625% bupivacaine alone; bupivacaine-only group: 0.125% bupivacaine alone). During the first stage of labor, 36 of 41 (88%) women in the bupivacaine-fentanyl group, and 37 of 39 (95%) women in the bupivacaine-only group, had analgesia of excellent or good quality (P = NS). During the second stage, 22 of 37 (59%) women in the bupivacaine-fentanyl group, and 23 of 35 (66%) women in the bupivacaine-only group, rated their analgesia as excellent or good (P = NS). Women in the bupivacaine-only group were more likely to have motor block at full cervical dilatation ($P < .001$). There was no significant difference between groups in duration of the second stage of labor, duration of pushing, position of the vertex before delivery, method of delivery, Apgar scores, or umbilical cord blood gas and acid-base values. The authors conclude that the continuous epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl produced analgesia similar to that provided by the infusion of 0.125% bupivacaine alone. However, the less intense motor block experienced by women in the bupivacaine-fentanyl group did not significantly shorten the second stage or result in a greater frequency of spontaneous delivery. (Key words: Anesthesia: obstetric. Anesthetic techniques: epidural. Local anesthetics: bupivacaine. Opioids: fentanyl.)

EPIDURAL ADMINISTRATION of an opioid alone has not consistently provided satisfactory analgesia during labor.[1–7] Epidural administration of a solution containing both local anesthetic and opioid may provide excellent analgesia.[8–15] Further, Naulty *et al.*[14] observed that the addition of butorphanol to a 0.25% solution of bupivacaine allowed a reduction in the subsequent dosage of local anesthetic and resulted in less intense motor block.

To our knowledge, only one study has compared the continuous epidural infusion (during labor) of local anesthetic and opioid with the infusion of local anesthetic alone. Skerman *et al.*[12] reported that parturients who received a continuous epidural infusion of 0.125% bupivacaine/0.00025% fentanyl experienced "stronger and more profound analgesia" than women who received an infusion of 0.125% bupivacaine alone. In contrast, we[16] earlier noted excellent intrapartum analgesia with continuous epidural infusion of 0.125% bupivacaine alone. We[16] also observed that infusion of 0.125% bupivacaine beyond a cervical dilatation of 8 cm prolonged the second stage of labor and increased the frequency of instrumental delivery in nulliparous women.

We posed the following questions: Would the addition of fentanyl to a dilute solution of bupivacaine result in analgesia similar to that provided by a higher concentration of bupivacaine alone? If yes, would infusion of the bupivacaine-fentanyl solution result in less motor block, a shorter second stage of labor, and a greater likelihood of spontaneous delivery than that resulting from infusion of the bupivacaine-only solution? The purpose of this study was to compare the effects following continuous epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl with those following infusion of 0.125% bupivacaine alone.

Materials and Methods

The protocol was approved by the University of Iowa Institutional Review Board for research involving human subjects. Written informed consent was obtained from healthy nulliparous women with term (≥36 weeks) singleton fetuses in the vertex presentation. Women with preeclampsia or insulin-dependent diabetes were excluded. Each fetus had a normal heart rate pattern before induction of epidural analgesia.

Each patient received an intravenous infusion of 750 ml of Ringer's lactate over 10–15 min before induction

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of epidural analgesia. When the cervix was 3–7 cm dilated, a catheter was inserted into the epidural space *via* the L3–4 interspace and advanced 3–4 cm cephalad. Each patient first received a test dose (3 ml of 0.5% bupivacaine with 1:200,000 epinephrine). Five minutes later, each patient received 6 ml of study solution 1 (bupivacaine-fentanyl group: 0.125% bupivacaine/0.0008% fentanyl;¶ bupivacaine-only group: 0.25% bupivacaine alone). Five minutes later, each patient received a continuous epidural infusion of study solution 2 at a rate of 12.5 ml/h (bupivacaine-fentanyl group: 0.0625% bupivacaine/0.0002% fentanyl;** bupivacaine-only group: 0.125% bupivacaine alone) (table 1).

Uterine displacement was maintained continuously, and each patient was encouraged to turn from side to side at 30-min intervals. The cephalad dermatomal level of anesthesia was determined by pinprick at 30-min intervals. The infusion rate was increased or decreased to maintain the sensory level at T10; if it was necessary to increase the rate of infusion, the patient first received an additional 2–5-ml bolus of study solution 2.

The maximal volume of study solution 2 was 50 ml. If the 50-ml syringe of study solution 2 became empty, a syringe of study solution 3 was substituted (bupivacaine-fentanyl group: 0.0625% bupivacaine alone, bupivacaine-only group: 0.125% bupivacaine alone). Thus, the maximal cumulative dosage of fentanyl was 150 μg (50 μg within the 6 ml of study solution 1, and 100 μg within the 50 ml of study solution 2).

Each syringe of coded study solution was freshly prepared by a hospital pharmacist according to a table of random numbers, and was administered in a double-blind manner. The patient, anesthesiologist, obstetrician, pediatrician, and nursing staff were unaware of any patient's group assignment.

The epidural infusion was discontinued when the cervix was noted to be fully dilated. Pushing was delayed for as long as 1 h in those patients who did not feel an urge to push.[17] One or two 5-ml boluses of study solution 3 were given to patients in whom perineal anesthesia was absent. No additional boluses of local anesthetic solution were administered to any patient until delivery.

At delivery, an epidural bolus of local anesthetic solution was administered only if the obstetrician had decided to perform operative delivery. Otherwise, pudendal block and/or perineal infiltration were performed as indicated. The obstetric staff had agreed that operative delivery would be performed for obstetric indications only; elective instrumental deliveries were not performed.

TABLE 1. Protocol

Time (Min)		Drug Given	
		Bupivacaine-fentanyl	Bupivacaine-only
0	3-ml test dose	0.5% bupivacaine with 1:200,000 epinephrine	0.5% bupivacaine with 1:200,000 epinephrine
5	6 ml of study solution 1	0.125% bupivacaine 0.0008% fentanyl (8 μg/ml of fentanyl)	0.25% bupivacaine
10	Study solution 2 at 12.5 ml/h (maximal volume = 50 ml)	0.0625% bupivacaine 0.0002% fentanyl (2 μg/ml of fentanyl, or 25 μg/h)	0.125% bupivacaine
	Study solution 3*	0.0625% bupivacaine	0.125% bupivacaine

* The syringe of study solution 3 was substituted if the 50-ml syringe of study solution 2 became empty. Also, one or two 5-ml boluses of study solution 3 were given to patients in whom perineal anesthesia was absent at full cervical dilatation.

The anesthesiologist asked each patient to indicate her pain score on an unmarked 100-mm visual analogue pain scale (0 = no pain, 100 = worst possible pain) at 0, 15, and 30 min after administration of the test dose, and then at 30-min intervals. Further, the anesthesiologist asked each patient to assess the quality of her analgesia during the first and second stages of labor. The first assessment ("How would you describe the quality of your pain relief since the epidural was begun—excellent, good, fair, poor, very poor?") was performed when the cervix was noted to be fully dilated. The second assessment ("How would you describe the quality of your pain relief during the time that you were pushing—excellent, good, fair, poor, very poor?") was performed immediately after delivery. If an epidural bolus of local anesthetic was administered for operative delivery, the second assessment of analgesia quality was performed before administration of the epidural bolus.

Maternal blood pressure was determined at 1-min intervals for 20 min, and subsequently at 15-min intervals, with an automated blood pressure monitor. Maternal hypotension was defined as a decrease in systolic blood pressure of ≥20%, or a systolic blood pressure < 100 mmHg. Hypotension was treated promptly by increasing the rate of intravenous fluid administration and by administering 5–10 mg of ephedrine intravenously.

The duration of the active phase of the first stage of labor was defined as the interval between cervical dilatation of 4 and 10 cm. The duration of the second stage of labor was defined as the interval between the diagnosis of full (10 cm) cervical dilatation and delivery.

¶ 8 μg/ml of fentanyl.
** 2 μg/ml of fentanyl, or 25 μg/h.

TABLE 2. Maternal Characteristics

	Bupivacaine-fentanyl n = 41	Bupivacaine-only n = 39	*P* Value
Age (yr)*	22 ± 4	22 ± 5	NS
Race			
Caucasian	40	39	NS
Black	1	0	
Childbirth preparation class			
Lamaze	20	15	NS
Health Department/ University	5	9	
None	16	15	
Weight (kg)*	80 ± 16	83 ± 16	NS
Height (cm)*	164 ± 6	165 ± 9	NS
Gestational age (weeks)*	39.8 ± 1.8	39.8 ± 1.6	NS
Cervical dilatation before epidural (cm)*	4.6 ± 0.9	4.6 ± 1.0	NS

NS = not significant.
* Mean ± SD.

Motor block was assessed according to the method of Bromage (none, partial, almost complete, complete).[18] The occurrence of maternal pruritus, nausea, emesis, and/or urinary retention was recorded. Neonatal assessment was by Apgar scores and umbilical venous and arterial blood gas and acid-base analysis.

TABLE 3. Conduct of Labor

	Bupivacaine-fentanyl n = 41	Bupivacaine-only n = 39	*P* Value
Duration of active phase of first stage (min)*†	381 ± 239	298 ± 180	NS
Duration of epidural infusion (min)*	315 ± 224	242 ± 175	NS
Dosage of bupivacaine (mg)*	67 ± 32	99 ± 49	<.001
Dosage of fentanyl (μg)*	132 ± 23	0	—
Motor block at end of epidural infusion at full dilatation†			
None	35 (95%)	14 (40%)	<.001
Partial	2 (5%)	13 (37%)	
Almost complete	0 (0%)	8 (23%)	
Complete	0 (0%)	0 (0%)	
Duration of second stage (min)*†	112 ± 64	124 ± 69	NS
Duration of pushing (min)*†	101 ± 64	103 ± 57	NS
Position of vertex immediately before delivery			
Occiput anterior	37 (90%)	33 (85%)	NS
Occiput posterior	3 (7%)	3 (8%)	
Occiput transverse	1 (2%)	3 (8%)	
Method of delivery			
Spontaneous	24 (59%)	24 (62%)	NS
Forceps	11 (27%)	8 (21%)	
Cesarean *before* full dilatation	4 (10%)	4 (10%)	
Cesarean *after* full dilatation	2 (5%)	3 (8%)	

NS = not significant.
* Mean ± SD.
† Excluding the four women in each group who underwent cesarean section before full cervical dilatation.

Statistical analysis was by Student's *t* test, Mann-Whitney U-test, Chi-square, and Fisher exact test as indicated. $P < .05$ was considered statistically significant.

Results

There were 41 patients in the bupivacaine-fentanyl group and 39 in the bupivacaine-only group. The two groups were similar with regard to age, race, childbirth preparation, weight, height, gestational age, and cervical dilatation before induction of epidural analgesia (table 2). Eight patients in the bupivacaine-fentanyl group, and ten in the bupivacaine-only group, had received an intravenous injection of meperidine or nalbuphine ≥ 1 h before induction of epidural analgesia (P = NS).

Conduct of Labor and Delivery

Fifteen patients in the bupivacaine-fentanyl group, and 13 in the bupivacaine-only group, were receiving intravenous oxytocin before induction of epidural analgesia (P = NS). Eleven patients in the bupivacaine-fentanyl group, and seven in the bupivacaine-only group, had intravenous oxytocin started after induction of epidural analgesia (P = NS).

Table 3 includes other data regarding conduct of labor. Although the two groups had similar cervical dilatation before induction of epidural analgesia, there was a tendency toward a longer active phase of the first stage of labor in the bupivacaine-fentanyl group ($P < .08$). Despite the longer epidural infusion in the bupivacaine-fentanyl group, the women in that group received significantly less bupivacaine than the women in the bupivacaine-only group ($P < .001$). Excluding the test dose, the mean (±SD) dosage of bupivacaine over time for women in the bupivacaine-fentanyl group was 10.6 ± 2.6 mg/h, *versus* 23.4 ± 6.6 mg/h for women in the bupivacaine-only group ($P < .0001$).

Women in the bupivacaine-only group were more likely to have motor block when the epidural infusion was discontinued at full cervical dilatation ($P < .001$) (table 3). However, there was no significant difference between the two groups in the duration of the second stage of labor, the duration of pushing, or the position of the vertex immediately before delivery.

Twenty-four women in each group underwent spontaneous vaginal delivery. Eleven women in the bupivacaine-fentanyl group, and eight in the bupivacaine-only group, underwent forceps delivery (P = NS). The indications for those forceps deliveries were: 1) failure to progress (five patients in the bupivacaine-fentanyl group, six in the bupivacaine-only group); and 2) fetal distress (six patients in the bupivacaine-fentanyl group, two in the bupivacaine-only group). Each patient with

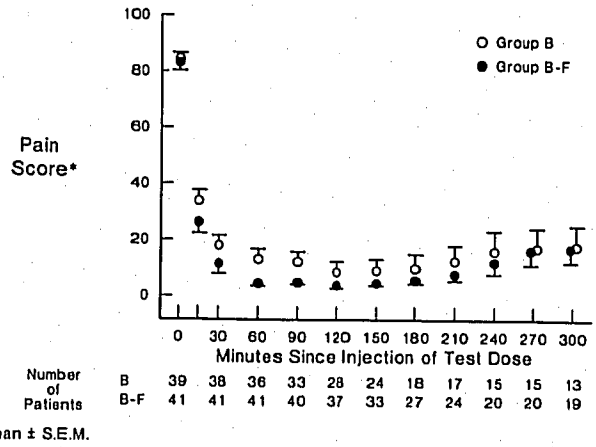

FIG. 1. Mean (±SEM) pain scores over time during the first stage of labor.

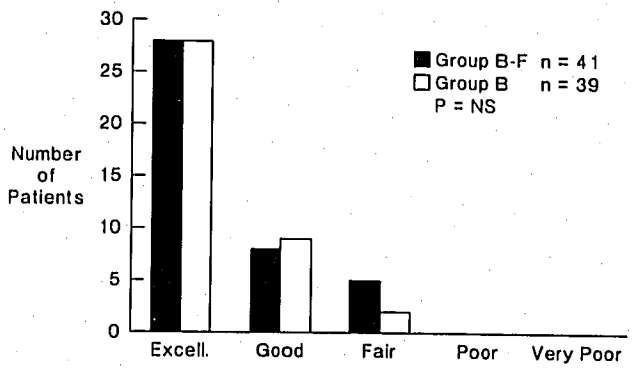

FIG. 2. Patient assessment of analgesia quality during the first stage of labor.

the diagnosis of failure to progress had a second stage of at least 120 min.

Four women in each group underwent cesarean section *before* full cervical dilatation (the diagnosis for one woman in the bupivacaine-fentanyl group was fetal bradycardia; the diagnosis for each of the other seven women was cephalopelvic disproportion). Two women in the bupivacaine-fentanyl group, and three in the bupivacaine-only group, underwent cesarean section *after* full cervical dilatation (the diagnosis for each of those women was cephalopelvic disproportion).

Analgesia Quality

Seventeen patients in each group received at least one bolus of 2–5 ml of study solution 2 after the continuous epidural infusion was begun. At the time that the epidural infusion was discontinued at full cervical dilatation, five patients in the bupivacaine-fentanyl group, and four in the bupivacaine-only group, had an infusion rate which was ≥15 ml/h.

The two groups were similar with regard to mean pain scores during the first stage of labor (fig. 1). Similarly, there was no significant difference between groups in patient assessment of analgesia quality during the first stage (fig. 2).

Nineteen of 37 (51%) patients in the bupivacaine-fentanyl group, and 22 of 35 (63%) in the bupivacaine-only group, had perineal anesthesia at full cervical dilatation and did not receive an epidural bolus of study solution 3 (P = NS). Among those women with perineal anesthesia at full cervical dilatation, six of 19 (32%) in the bupivacaine-fentanyl group, and nine of 22 (41%) in the bupivacaine-only group, did not have an urge to push and had delayed pushing (P = NS). Among the women who received a bolus of study solution 3, two of 18 (11%) in the bupivacaine-fentanyl group, and three of 13 (23%) in the bupivacaine-only group, temporarily lost the urge to push and had delayed pushing (P = NS).

Among the women who delivered vaginally, seven of 35 (20%) in the bupivacaine-fentanyl group, and eight of 32 (25%) in the bupivacaine-only group, retained surgical perineal anesthesia at delivery, without administration of pudendal block, perineal infiltration, or an epidural bolus of known local anesthetic solution (P = NS). Similarly, there was no significant difference between the two groups in patient assessment of analgesia quality during the second stage of labor (fig. 3). Although the epidural infusion was not continued during the second stage, 22 of 37 (59%) women in the bupivacaine-fentanyl group, and 23 of 35 (66%) women in the bupivacaine-only group, rated their second stage analgesia quality as excellent or good (P = NS).

Women in the bupivacaine-fentanyl group were more likely to experience pruritus than women in the bupivacaine-only group ($P < .05$) (table 4). No woman in either group requested treatment for pruritus. The two groups were similar with regard to incidence of nausea and emesis. There was a tendency toward a greater incidence of urinary retention in the bupivacaine-fentanyl group ($P < .08$).

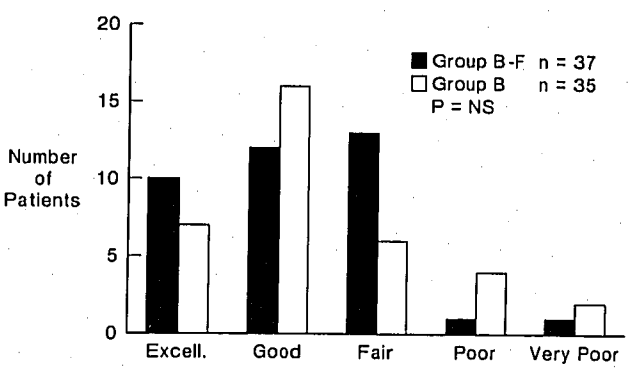

FIG. 3. Patient assessment of analgesia quality during the second stage of labor.

TABLE 4. Side Effects

	Bupivacaine-fentanyl n = 41	Bupivacaine-only n = 39	*P* Value
Pruritus	9 (22%)	2 (5%)	<.05
Nausea	11 (27%)	12 (31%)	NS
Emesis	7 (17%)	8 (21%)	NS
Urinary retention	26 (63%)	17 (44%)	NS

NS = not significant.

EFFECTS ON THE FETUS AND NEONATE

Six patients in the bupivacaine-fentanyl group, and two in the bupivacaine-only group, had transient hypotension during the first hour after induction of epidural analgesia (*P* = NS). Four patients in the bupivacaine-fentanyl group, and no patient in the bupivacaine-only group, had transient hypotension thereafter (*P* = NS). There were abnormal fetal heart rate patterns in the fetuses of eight patients in each group, which prompted determination of fetal scalp blood *p*H during the interval between induction of epidural analgesia and delivery.

There were no significant differences between groups in infant weight, incidence of meconium-stained amniotic fluid, Apgar scores, or umbilical cord blood gas and acid-base values (table 5). Mean umbilical venous and arterial blood *p*H values for all infants delivering by vertex presentation in our hospital are 7.32 and 7.24, respectively (Van de Wetering M, Senden I: Unpublished data). One infant in the bupivacaine-fentanyl group, and two infants in the bupivacaine-only group, received naloxone within 1 h of birth.

TABLE 5. Newborn Assessment

	Bupivacaine-fentanyl n = 41	Bupivacaine-only n = 39	*P* Value
Infant weight (gm)*	3394 ± 418	3435 ± 407	NS
Meconium-stained amniotic fluid	16 (39%)	12 (31%)	NS
1-min Apgar ≥ 7	34 (83%)	32 (82%)	NS
5-min Apgar ≥ 7	41 (100%)	39 (100%)	NS
Umbilical venous blood analysis*			
*p*H	7.33 ± .05	7.32 ± .07	NS
P_{O_2} (mmHg)	27.9 ± 6.4	27.2 ± 7.5	NS
P_{CO_2} (mmHg)	36.4 ± 4.6	37.4 ± 5.2	NS
Base excess (mEq/L)	−5.5 ± 1.8	−5.5 ± 2.9	NS
Umbilical arterial blood analysis*			
*p*H	7.25 ± .05	7.22 ± .08	NS
P_{O_2} (mmHg)	15.5 ± 5.5	16.0 ± 9.0	NS
P_{CO_2} (mmHg)	45.8 ± 5.6	47.2 ± 8.2	NS
Base excess (mEq/L)	−6.1 ± 2.2	−7.4 ± 4.3	NS

NS = not significant.
* Mean ± SD.

DISCUSSION

Heretofore, anesthesiologists have cautioned obstetricians regarding systemic administration of opiates during labor.[19] Therefore, we should document tangible benefits of intrapartum epidural opioid administration before recommending widespread use of the technique. In the present study, infusion of the bupivacaine-fentanyl combination resulted in analgesia similar to that provided by infusion of a higher concentration of bupivacaine alone. Women in the bupivacaine-fentanyl group experienced less intense motor block, but they did not have a significantly shorter second stage or a greater frequency of spontaneous delivery. It is possible that we might have noted an inter-group difference in outcome had we continued the epidural infusion until delivery. In an earlier study,[16] we noted that epidural infusion of 0.125% bupivacaine beyond a cervical dilatation of 8 cm prolonged the second stage of labor, and increased the frequency of instrumental delivery in nulliparous women, when compared with replacement of the bupivacaine with placebo. In our judgement, those results precluded our continuing the epidural infusion until delivery in the present protocol. Undoubtedly, some patients in the present study had inadequate second stage analgesia because the epidural infusion was discontinued at full cervical dilatation. In practice, we continue the epidural infusion until delivery in some, but not all, patients.

Although women in the bupivacaine-fentanyl group did not have an increased frequency of spontaneous delivery, the less intense motor block remains a tangible benefit. Most parturients consider paralysis during labor to be unpleasant. Obstetric nurses also prefer that their patients retain motor function to facilitate nursing care. Our nurses' most frequent complaint regarding epidural analgesia is that patients are unable to move themselves. In the present study, only two of 37 (5%) patients in the bupivacaine-fentanyl group had clinically detectable motor block when the epidural infusion was discontinued at full cervical dilatation.

We did not expect to observe a nearly significant increase in duration of the active phase of the first stage of labor in the bupivacaine-fentanyl group. Aside from the borderline statistical significance, we hesitate to ascribe clinical significance to this result for three reasons. First, assessment of the duration of the first stage was not a primary focus of this study. Second, it is often difficult to determine accurately the duration of either the first stage or the active phase of the first stage. The definition of the active phase used in this study is convenient, but it is not an appropriate definition for every patient. For example, 60% of normal patients have entered the active phase by 4-cm cervical dilatation, and

89% have entered the active phase by 5-cm dilatation.[20] Third, Cohen *et al.*[13] reported a *shorter* first stage in women who received a bolus injection of bupivacaine (22.5 mg) and fentanyl (50 or 100 μg), compared with women who received either bupivacaine alone (22.5 mg) or bupivacaine (7.5 mg) and fentanyl (100 μg). They speculated that the former patients may have had reduced catecholamine release as a consequence of "better relief of pain and anxiety."[13] Additional prospective studies are needed to clarify whether epidural administration of bupivacaine and fentanyl affects the duration of the first stage of labor.

Not unexpectedly, women in the bupivacaine-fentanyl group were more likely to experience pruritus.[4,8,9,11,13] The pruritus was mild, and no patient requested treatment. In addition, there was a nearly significant tendency toward a greater incidence of urinary retention in the bupivacaine-fentanyl group. It is unclear whether that resulted directly from the epidural administration of fentanyl, or indirectly from the longer first stage of labor in the bupivacaine-fentanyl group.

Cohen *et al.*[13] observed that infants exposed to a maternal epidural bolus of 50 or 100 μg of fentanyl had similar neurobehavioral scores when compared with infants exposed to a bolus of bupivacaine alone. Similarly, Capogna *et al.*[21] reported that the addition of approximately 100 μg of fentanyl to epidural bupivacaine did not significantly affect the neurobehavioral scores of newborn infants. In the present study, infants in the bupivacaine-fentanyl group were not more likely to have low Apgar scores or to receive naloxone than infants in the bupivacaine-only group. We did not perform neurobehavioral testing, and cannot exclude the possibility of subtle changes in newborn behavior in the bupivacaine-fentanyl group. However, we considered such changes to be unlikely because the maximal cumulative dosage of fentanyl was limited to 150 μg administered over 3–4 h.

We conclude that the continuous epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl produced analgesia similar to that provided by the infusion of 0.125% bupivacaine alone. Women in the bupivacaine-fentanyl group experienced less intense motor block, but they did not have a significantly shorter second stage or a greater frequency of spontaneous delivery.

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