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Original Article

Epinephrine on Continuous Epidural Pain Relief in Labor

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ABSTRACT

Background: Epidural pain relief in labor is commonly provided by a combination of local anesthetic and opioid. The opioid allows for a reduction in the concentration of local anesthetic, thus reducing side effects, while maintaining effective pain control. Epinephrine is an analgesic medication that may also improve pain control.

Methods: We conducted a prospective, randomized, double-blind study comparing an epidural infusion of bupivacaine 0.04%, fentanyl 1.66 µg/mL at a rate of 15 mL/h. Women were randomized to that solution (BF) or to the addition of epinephrine 1.67 µg/mL (BEF). Both solutions were administered at a rate of 15 mL/h. The primary outcome was the hourly frequency of breakthrough labor pain.

Results: A total of 120 women were enrolled, and 100 completed the trial. On average, women had one episode of breakthrough pain throughout the course of their labor, with women who received epinephrine having fewer episodes (BF: 1.3 ± 1.1 vs. BEF: 0.7 ± 0.9; P = 0.002). The hourly rate of breakthrough pain was 52% lower in the group that received epinephrine (BF: 0.12 ± 0.15 vs. BEF: 0.25 ± 0.22; P = 0.002). There no differences between groups in pain scores or in side effects. Epinephrine did not affect the duration of labor with epidural analgesia (BF: 464 ± 310 min vs. BEF: 393 ± 214 min; P = 0.48).

Conclusion: The addition of a small amount of epinephrine to a low concentration, high volume epidural solution improves pain control and reduces the rate of breakthrough pain by half. There is no difference in side effects compared to a solution without epinephrine. (Funded by the Beth Israel Anesthesia Foundation, Boston, USA.)

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Ideal labor analgesia would provide high-quality pain control with minimal adverse effects on the mother and fetus. Local anesthetics administered via an epidural catheter provide effective labor pain control; however, the high concentration that is required results in undesirable including side effects of hypotension, sensory and motor block. These side effects are dose-dependent, and the incidence and severity can be reduced by decreasing the concentration of local anesthetic (1). The addition of an adjuvant, such as fentanyl, allows a reduction in the concentration of local anesthetic required to produce analgesia (2). Importantly, the reduction in local anesthetic concentration does not sacrifice pain control or maternal satisfaction.

Epinephrine prolongs and enhances the effect of local anesthetics in the spinal and epidural space. When used for the initiation of labor analgesia, epinephrine reduces the minimum local analgesic concentration (MLAC) of epidural bupivacaine by 30% (3), possibly due to a spinal adrenergic mechanism. Breen, et al. first reported the use of an epidural solution containing a very low concentration of bupivacaine, 0.04%, combined with fentanyl and epinephrine (4). The subjects reported good pain control and the majority maintained the ability to ambulate. A more recent report demonstrated that patients who received this very low concentration solution did not require significantly more management by the anesthesia team than patients who received a more traditional, high concentration local anesthetic solution (1). We presume that the successful pain control achieved with the very low concentration of bupivacaine was due to the combination with both fentanyl and epinephrine as adjuvants; however, the effectiveness of epinephrine as an adjuvant has not been well studied. Furthermore, the effectiveness of an epidural solution containing epinephrine on continuous pain control during labor has received minimal attention. The aim of our study was to assess whether the addition of epinephrine to epidural solution containing bupivacaine and fentanyl could decrease breakthrough pain during labor.

METHODS

This prospective, double-blind, randomized study was approved by the Beth Israel Deaconess Medical Center institutional review board for research ethics. All healthy, ASA II parturients in active labor were eligible to participate. Inclusion criteria were singleton gestation, vertex presentation, less than 7 cm cervical dilation, and requesting epidural analgesia for labor pain. Exclusion criteria were previous opioid use, chronic pain, diabetes, or significant fetal anomalies or fetal demise.

After enrollment, and written, informed consent, subjects received a combined-spinal epidural (CSE). The CSE was performed at the L3-L4 or L4-L5 interspaces by an experienced fellow or resident under the supervision of an attending anesthesiologist. Spinal injectate consisted of 2 mg bupivacaine and 12.5 μg fentanyl. A three-port, side-holed epidural catheter (Portex, Keene, NH) was then threaded to 5 cm into the epidural space, and a test-dose consisting of 3 mL of lidocaine 1.5% and epinephrine 5 μg/mL was given.

After ensuring a negative test-dose, the study solution of epidural medication was initiated in a double-blinded fashion. Randomization for group assignments was created by a computer-generated table and maintained on individual folded cards inside consecutively numbered and sealed opaque envelopes. A physician who was not part of the patient' s care or follow-up opened the envelope and prepared the study solution.

· BF: bupivacaine 0.04%, fentanyl 1.66 μg/mL at a rate of 15 mL/h, or

· BEF: bupivacaine 0.04%, fentanyl 1.66 μg / mL, epinephrine 1.67 μg/mL at a rate of 15 mL/h.

Neither group was able to self-administer supplemental epidural boluses (i. e. patient-controlled epidural analgesia, PCEA) so that we could accurately assess the nature of their breakthrough pain. Vital signs, verbal pain scores (VPS), sensory level, motor block, and side effects were recorded at placement and at 15-minute intervals for the first 30 min and at 30-minute intervals until 120 minutes. VPS was measured using an 11-point scale ranging from 0 for no pain to 10 for the worst pain imaginable. Motor block was evaluated using the modified Bromage scale (0 = no motor block; 1 = inability to extended the leg, able to move the knees

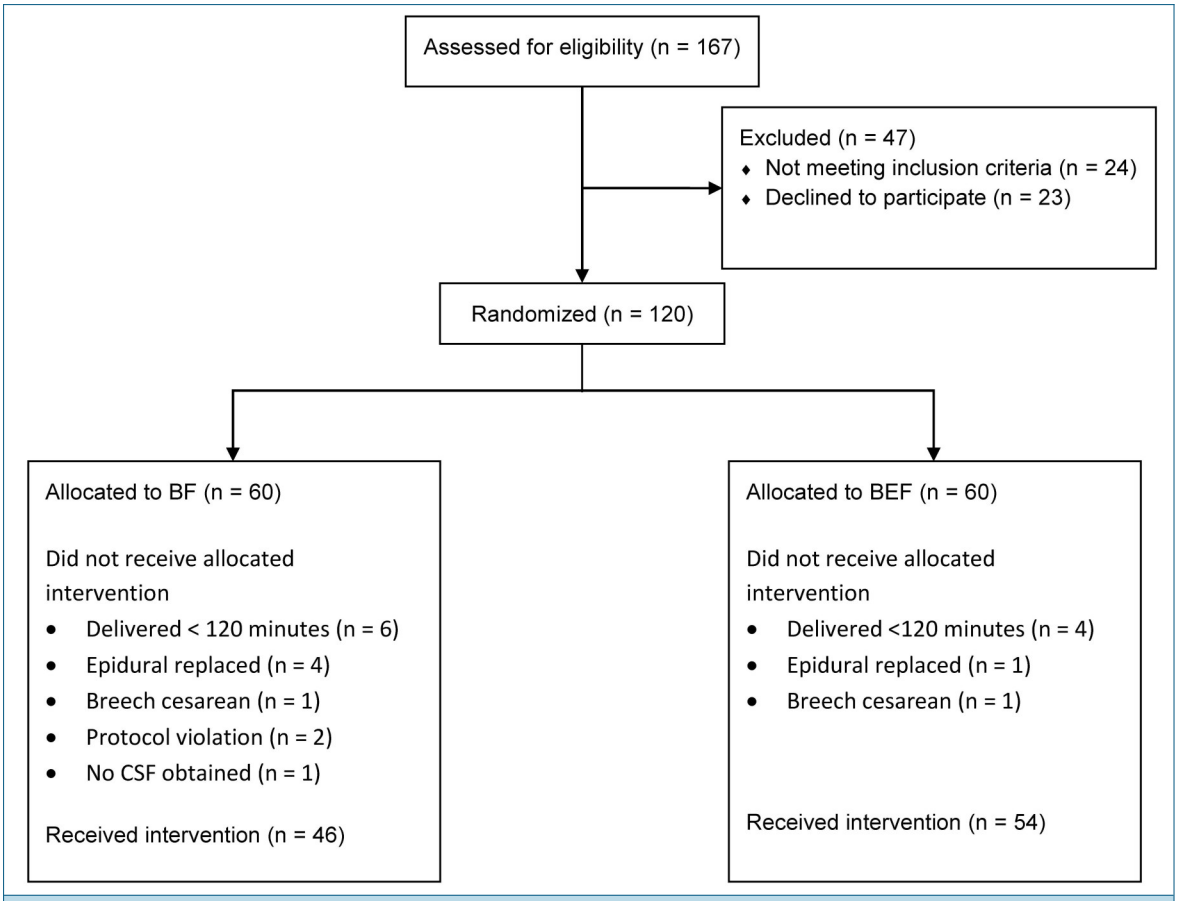

Figure 1. Flowchart of Patient Enrollment, Randomization, and Study Completion.

and feet; 2 = inability to increase the extended leg and to move the knees, able to move the feet; 3 = partial block (just able to move the knees); 4 = slight weakness with hip flexion; 5 = no detectable block with hip flexion). Hypotension was defined as systolic pressure decreased by 30% from baseline or less than 80 mm Hg with symptoms.

The primary outcome for this study was the average hourly rate of breakthrough labor pain, calculated by the number of episodes divided by the duration of epidural analgesia. An episode of breakthrough pain was defined as pain or pressure occurring with contractions while receiving epidural analgesia and relieved by supplemental medication. At each episode of breakthrough pain, the VPS, pain location, level of sensory block and medications given were recorded. Treatment of an episode of breakthrough pain was based on the following protocol:

I. Assessment of the epidural catheter position and sensory level:

a. Administration of 8 mL of bupivacaine 0.125%, fentanyl 100 μg;

b. If no relief after 15 minutes: administration of 10 mL of bupivacaine 0.125%;

c. If no relief after 15 minutes: administration of 10 mL of bupivacaine 0.125%;

d. If no relief after 15 minutes: further assessment and decision to replace the catheter by the anesthesia care team.

II. With the third episode of successfully treated breakthrough pain, the epidural solution would be increased to bupivacaine 0.08%, fentanyl 3.33 μg/mL at a rate of 15 mL/h.

III. After the sixth episode of breakthrough pain, the epidural solution would be increased to bupivacaine 0.125%, fentanyl 3.33 μg/mL at a rate of 15 mL/h.

Subjects whose pain was not adequately re-

Table 1. Baseline Demographic and Obstetric Characteristics.

Characteristic	Group BF	Group BEF	P Value
Age (yr)	31.7 ± 4.7	31.5 ± 5.0	0.84
Height (cm)	163.8 ± 7.4	162.3 ± 6.6	0.28
Weight (kg)	79.2 ± 11.6	78.0 ± 13.6	0.64
Gestational age (wk)	39 (38 to 40)	39 (38 to 40)	0.61
Nulliparity	25 (54%)	29 (54%)	1.0
TOLAC	1 (2%)	4 (7%)	0.37
Oxytocin	27 (59%)	33 (61%)	0.84
Cervical dilation (cm)	3.5 (3 to 4)	3 (3 to 4)	0.94
VPS before placement	8 (7 to 9)	8 (7 to 9)	0.57
Cesarean Delivery	8 (18%)	12 (24%)	0.62
Neonatal Weight (g)	3580 ± 475	3350 ± 490	0.03 *

BF, bupivacaine-fentanyl solution; BEF, bupivacaine-epinephrine-fentanyl solution; TOLAC, Trial of Labor After Cesarean; VPS, Verbal Pain Score.
All values reported as mean ± standard deviation, median (interquartile range), or number (percentage).

Table 2. The frequency of Breakthrough Labor Pain During Epidural Analgesia.

	Group BF	Group BEF	P Value
Breakthrough pain	1.3 ± 1.1	0.7 ± 0.9	0.002 *
Duration (min)	464 ± 310	393 ± 214	0.48
BTP Rate	0.25 ± 0.22	0.12 ± 0.15	0.002 *
Replacement	4 (6.7%)	1 (1.7%)	0.21
VPS			
15 min	0 (0 to 0)	0 (0 to 0)	0.66
30 min	0 (0 to 0)	0 (0 to 0)	0.36
60 min	0 (0 to 0)	0 (0 to 0)	0.66
90 min	0 (0 to 2)	0 (0 to 0.25)	0.28
120 min	0 (0 to 3)	0 (0 to 1)	0.08
Hypotension	3 (6.5%)	6 (11.1%)	0.50
Nausea	1 (2.2%)	0 (0%)	0.46
Pruritus	4 (8.7%)	4 (7.8%)	1.0

BF, bupivacaine-fentanyl solution; BEF, bupivacaine-epinephrine-fentanyl solution; VPS, Verbal Pain Score.
Breakthrough pain represents the number of episodes of pain that were successfully and completely treated; Duration spans time of neuraxial placement to delivery of the neonate; BTP rate is the number of episodes of breakthrough pain per hour throughout labor; Replacement is the number of epidural catheters that failed requiring replacement from the complete cohort (n = 20); VPS are times after neuraxial placement.
All values reported as mean ± standard deviation, median (interquartile range).

lieved by the initial spinal dose, whose episode of breakthrough pain was not relieved by supplemental medications, or who required epidural catheter replacement were excluded from further analysis. Subjects who delivered within 2 hours of placement were eliminated from the analysis, the epidural infusion would not have been determined to be effective yet.

Statistical Analysis

Data are reported as mean ± standard deviation, median (Inter-quartile range, IQR), or incidence of group, as appropriate. Baseline demographic and obstetric characteristics were compared to ensure that the groups were similar. Outcomes were compared on a protocol-compliant basis because of the small number of dropouts and because the primary outcome would be severely affected by a failed epidural catheter or a short duration of analgesia. Comparisons for normally distributed variables were performed using the t-test, the Mann-Whitney test was used for those that lacked a normal distribution, and Fisher's exact test or incidence, as appropriate. The Komolgorov-Smirnov test was used to assess the distribution of the data.

Apriori sample size of 60 subjects per group was determined to have an alpha error of 0.05, and 80% power to detect a 40% difference between the two groups, assuming a Poisson distribution of the data. Statistical significance was determined at P-value of $\leqslant 0.05$. Data were analyzed using NCSS 11 Statistical Software (2016, Kaysville, UT, USA).

RESULTS

A total of 120 parturients enrolled in the study and 100 completed the protocol for analysis (Figure 1). Ten patients delivered within 120 minutes of neuraxial placement; five subjects had the epidural catheter replaced (one due to accidental dural puncture with the epidural needle, and four due to failure to treat breakthrough pain); two subjects were determined to be breech shortly after placement and proceeded to cesarean delivery; two were eliminated due to protocol violations (the patient administered bolus button was reattached by the nurse); one due to inability to obtain cerebral spinal fluid with the spinal needle. Of the remaining 100 subjects, 46 were in the BF group, and 54 in the BEF group. The groups had similar demographic and obstetric characteristics except for a larger neonatal weight in the BF group (Table 1).

We found no difference in the pain scores af-

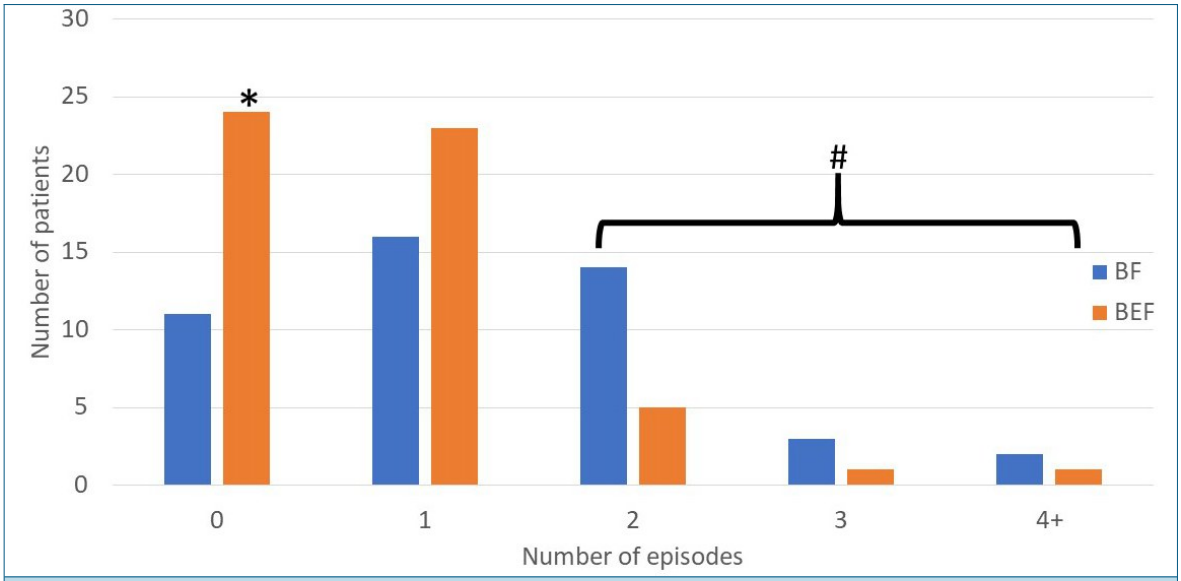

Figure 2. Number of Episodes of Breakthrough Pain by Group.
A total of 24 (44%) of the BEF group did not experience a breakthrough pain compared with 11 (24%) of the BF group (denoted by *; P = 0.4). The BF group was also more likely to experience more than one episode (41% vs. 13%); denoted by #; P = 0.003).

ter initiation of combined-spinal analgesia (Table 2). The BEF group was more likely to never experience an episode of breakthrough pain than the BF group (BEF 24 / 54 (44%) vs. 11 / 46 (24%); P = 0.04). Also, the BEF group was less likely to experience more than one episode (13% vs. 41%, P = 0.003). The BEF group experienced fewer episodes of breakthrough pain than the BF group (Table 2 and Figure 2) and had a lower frequency of breakthrough pain, which was our primary outcome. The duration of labor after initiating epidural pain control was similar between groups. We found no differences in secondary outcomes, including hypotension, nausea and pruritus. The rate of cesarean delivery was also similar between groups (Table 1).

DISCUSSION

We found that the addition of epinephrine to a low-dose bupivacaine-fentanyl epidural infusion significantly decreased the frequency of breakthrough pain during epidural analgesia. In fact, we saw a 50% reduction in the frequency with which women requested additional pain medicine. Importantly, this improvement in continuous pain control was not associated with any identifiable side effects such as hypotension, nausea, or difference in labor outcomes such as prolongation of labor or cesarean delivery. Connelly et al. found a longer time to first request for supplemental analgesia and lower pain scores at 2.5 and 4.5 hours when epinephrine was added to a continuous infusion of a low concentration of bupivacaine and fentanyl; however, they did not examine the effect of epinephrine on the success of pain control throughout labor (5). That study added epinephrine 5 μg/mL at a rate of 10 mL/hr, delivering 50 μg per hour. Our study delivered only 25 μg of epinephrine per hour. This would suggest that the addition of a small amount of epinephrine to a low concentration of the local anesthetic epidural solution can significantly improve pain control without side effects. Okutomi et al. demonstrated that epinephrine administered in the spinal fluid reduced the frequency of supplemental requests for treatment of breakthrough pain during subsequent labor epidural analgesia (6). These authors found that spinal epinephrine increased motor block. We hypothesize that this may be a reflection of an additive effect of epinephrine with the local anes-

thetic, which is similar to the additive effect of fentanyl on local anesthetics. Unlike in our study, the increase in the motor block may have become clinically significant due to the higher concentration used in their labor epidural solution (0.1% bupivacaine). A similar finding was noted by Cohen et al. when examining the ability of women to ambulate based on the concentration of bupivacaine in the epidural solution (7).

The mechanism of analgesic augmentation of local anesthetics is not definitively known, but has been hypothesized to be due to either alpha-1 or alpha-2 adrenergic receptor activity (8, 9). Epinephrine has activity at a number of receptors, and the activation of these receptors in the cardiovascular system is certainly dose-dependent. However, in the neural axis the concept of dose dependency may not be relevant, but instead, the focus should be on which receptors are found in the local environment. Studies have demonstrated that the concentration of alpha-1 and alpha-2 receptors decreases quantity in the small vascular of the central nervous system, preventing vasoconstriction during periods of stress (10). Goodman et al. added low dose (100 μg) of spinal epinephrine administered with bupivacaine or fentanyl, either alone or in combination (9). They found that epinephrine did not significantly prolong the duration of spinal analgesia or either bupivacaine or fentanyl but resulted in severe nausea. This is consistent with a lack of alpha-1 adrenergic activity by a low dose of spinal epinephrine.

We believe that epinephrine improves epidural labor analgesia through its alpha-2 adrenergic activity. The alpha-2 adrenergic receptor is well described in the pain-transmission system in the dorsal horn of the spinal cord where it produces analgesia (11). The administration of 100 μg of epinephrine in saline – with no additional medications – has been shown to produce a segmental analgesia to pinprick (12). Both epinephrine and norepinephrine result in hyperpolarization of afferent nerve terminals in the dorsal horn, and this effect is reversed by alpha-2 antagonist, but not alpha-1 or beta-adrenergic receptor antagonists (13). In addition to epinephrine, clonidine has potent alpha-2 receptor activity. Epidural clonidine is approved for refractory chronic pain, but this medication carries a "Black Box" warning in pregnancy due to its side effects of hypotension and sedation, which are all undesirable in pregnancy (12). Dexmedetomidine has greater specificity for the alpha-2 adrenergic receptor; while several small studies have reported both epidural and spinal administration in humans, this medication has not yet been shown to be safe for use in the neuraxis.

There are certain limitations to our study that can be identified. First, all patients received a CSE, which overall has a lower incidence of breakthrough pain compared with other modalities (14, 15). This was done to attempt to standardize the pain relief to each study parturient within the first 90 minutes so that the analgesic effect of the epidural solution throughout the course of labor could be studied. In addition, the maternal request for boluses was used as an indicator for breakthrough pain. This could be influenced by previous experience, anxiety and psychosocial factors which were not taken into consideration in the analysis of data. We believe that the rate of breakthrough pain may be a reliable comparison tool for epidural infusion comparisons; we note that the rate among the placebo groups is similar to the rate found in a previous study (16). We did find a small but statistically significant difference of 230 g in neonatal weight, and the fetal weight has been shown to be a weak predictor of breakthrough pain (15). The differences in our study were small, and we do not believe clinically significant, but worth considering. Finally, some practitioners may feel that the combination of three drugs in the epidural solution could lead to further complications including increased risk of a drug error. We feel that this risk and increase in work may be worth taking if there is a decrease in side effects in comparison with adding narcotics or using local anesthetics alone. Thus far, no ideal combination of medications in the epidural solution has been identified. There may be an advantage of combining the rapid narcotic effect of fentanyl with the adrenergic effects of epinephrine.

In conclusion, epinephrine 1.67 μg/mL added to bupivacaine 0.04% and fentanyl 1.66 μg/mL epidural solution appeared to increase the effectiveness of labor analgesia. There were no significant increases in side effects and there was a decrease in the incidence of breakthrough pain. A

low dose of epinephrine may be a useful adjuvant to epidural solutions in patients that are known to be at increased risk for breakthrough pain without increasing other side effects.

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The authors have no other potential conflicts of interest for this work.

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