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Original Article

Fentanyl and Epinephrine on the Minimum Local Analgesic Concentration of Epidural Bupivacaine for Labor Pain Relief

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ABSTRACT

Background: Epidural local anesthetic medications are effective in producing labor pain relief, but the high concentrations required result in significant maternal side effects. The concentration of local anesthetic can be reduced by the addition of an opioid medication. Epinephrine can also act as an analgesic medication in addition to causing vasoconstriction. If epinephrine improves the initiation of pain control by analgesic mechanism might allow for a further reduction of the minimum local analgesic concentration (MLAC).

Methods: We conducted a randomized, double-blind, prospective dose-response study examining the initiation of labor pain relief in parturients with epidural catheters. Subjects were randomized to one of four groups: bupivacaine, bupivacaine-fentanyl 1.67 μg/mL, bupivacaine-epinephrine 1.67 μg/mL, and bupivacaine-fentanyl-epinephrine. We used the up-down sequential allocation technique to determine the MLAC of bupivacaine in each group. MLAC calculation was performed with the equation of Massey and Dixon and confirmed with probit analysis.

Results: We found that the MLAC of bupivacaine alone (0.119% ± 0.07%) was reduced when either fentanyl (0.048% ± 0.03%) or epinephrine (0.082% ± 0.05%) were added. The MLAC of bupivacaine was reduced further by the combination of both epinephrine and fentanyl (0.033% ± 0.02%). There were no significant side effects in either group.

Conclusion: The addition of either fentanyl, epinephrine or both medications in an epidural solution can reduce the effective dose of bupivacaine for the initiation of labor pain relief. The addition of these adjuvants allows for a further reduction of the concentration of bupivacaine, thereby reducing side effects. (Funded by the Beth Israel Anesthesia Foundation, Boston, USA.)

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Local anesthetics are the most effective class of epidural analgesia medications used to treat labor pain. These medications, commonly bupivacaine and ropivacaine, decrease nerve conduction through the radicular nerves, and also likely affect the transmission of pain signals in the spinal cord (1, 2). While epidural local anesthetic medications can be used as sole agents, the doses required often result in undesirable side effects. These side effects include hypotension, excessive motor and sensory blockade, and a potential for local anesthetic toxicity. By adding other classes of analgesic medications, the effective dose of local anesthetic can be reduced, which lessens the severity and frequency of side effects. Opioid medications have been demonstrated to reduce the local anesthetic requirements for pain in animal models (3), and epidural labor pain control in a dose-dependent fashion(4). Lower concentrations of local anesthetic in the epidural solution result in a lower incidence of hypotension and motor blockade (5). However, local anesthetic side effects remain a concern even in low concentration solutions.

Epinephrine is a medication that has been shown to aid pain relief when added to epidural medications (6, 7), but inconsistent findings with spinal administration (8, 9). The nature of this improvement in pain relief is not precisely defined, and the mechanism could have an implication in the severity of local anesthetic side effects. One possibility is that epinephrine acts primarily via alpha-1 adrenergic activity, resulting in vasoconstriction of the epidural blood vessels. This would decrease the elimination of local anesthetic, and in the long run, would increase the side effects. The other possibility is that epinephrine produces pain relief via a spinal cord mechanism – alpha-2 adrenergic receptors have been shown to produce analgesia. In this case, adding epinephrine might be beneficial as it could allow for further reducing the minimum local analgesic concentration (MLAC), and potentially lesser frequency of side effects.

The MLAC in obstetrics has been defined as the median effective local analgesic concentration in a 20 mL volume for epidural analgesia in the early stage of labor (4). We hypothesized that the addition of epinephrine to epidural bupivacaine would reduce the MLAC required to initiate epidural pain relief. If epinephrine acts via the alpha-2 adrenergic mechanism, then this reduction should also be demonstrated when epinephrine is added to a mixture of local anesthetic and opioid, as vasoconstriction should have no effect on the initiation of analgesia provided by a local anesthetic and a lipophilic opioid. Thus, we conducted this dose-finding study to determine whether 1) epinephrine reduces the MLAC of bupivacaine for the initiation of epidural labor analgesia, and 2) epinephrine reduces the MLAC of bupivacaine in the presence of fentanyl.

METHODS

This double-blind, randomized study was approved by the institutional review board for research ethics at Beth Israel Deaconess Medical Center (Committee on Clinical Investigations), Boston, MA, United States. Potential subjects were approached for inclusion in early labor, prior to experiencing significant pain. All subjects who agreed to participate signed a written informed consent for study participation. Inclusion criteria were ASA physical status 2, term, singleton pregnancy in the vertex position, with a desire to have epidural pain control for labor. The patient's cervical dilation had to be $\leqslant 5$ cm at the request for epidural pain relief. Exclusion criteria included the use of opioids within 4 hours of placement, chronic opioid use, or allergy to receive any study medication.

Randomization was performed using a computer-generated list, with allocation maintained in sealed, consecutively numbered, opaque envelopes. When the patient requested epidural pain relief for their labor pain, the envelope was opened, and an anesthesiologist not involved in the study would mix a syringe for the patient to the randomized medication. Patients would receive either bupivacaine (BUP), bupivacaine with 1.67 μg/mL of fentanyl (BUP-FEN), bupivacaine with 1.67 μg/mL of epinephrine (BUP-EPI), or bupivacaine with 1.67 μg/mL of fentanyl and 1.67 μg/mL of epinephrine (BUP-FEN-EPI). We chose the concentrations used in this study based on the experience at our center over many years (10). While the concentration of epinephrine is below that reported by Polley, et al. and

Table 1. Baseline Demographic and Obstetric Factors of the Four Groups of Subjects.

Characteristic	Group Bup	Group Bup-Fen	Group Bup-Epi	Group Bup-Fen-Epi	P Value
Age (yr)	31.0 ± 5.4	30.9 ± 5.1	30.3 ± 4.1	31.7 ± 5.9	0.69
Height (cm)	162 ± 7	162 ± 11	163 ± 7	163 ± 7	0.91
Weight (kg)	80.6 ± 16.5	80.6 ± 17.5	83.2 ± 20.3	78.2 ± 10.9	0.36
Nulliparous	25 (63%)	25 (63%)	23 (58%)	28 (70%)	0.71
Gestational Age (wk)	38.5 (38 to 40)	38 (38 to 40)	38 (38 to 40)	38 (38 to 40)	0.49
Induction	16 (41%)	17 (43%)	20 (50%)	25 (64%)	0.39
NVD	32 (80%)	31 (78%)	31 (78%)	34 (85%)	0.81
VAS Pain	7 (6 to 9)	7 (6 to 8)	8 (7 to 10)	7 (5 to 8)	0.09

NVD, normal vaginal delivery; VAS, visual analogue scale.
NVD with remainder being assisted vaginal or cesarean deliveries. VAS Pain is the pain score obtained immediately prior to placement of epidural catheter.
Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage of group).

commonly supplied by pharmaceutical companies, no dose-response study has yet been performed to compare analgesia, and our clinical experience was that this concentration had a significant impact on pain relief (11). Similarly, the concentration of fentanyl was chosen based on our experience with successful pain relief and a low incidence of side effects. Both of these concentrations are created by adding 100 μg of the medication into a 60 mL syringe.

The MLAC of bupivacaine was determined using the up-down, sequential allocation methodology described by Massey and Dixon (12). Briefly, the initial patient in each group would receive 20 mL of an epidural study solution containing a predetermined concentration of bupivacaine. Based on the success or failure of that concentration at relieving labor pain, the subsequent patient would receive a concentration of bupivacaine that would be increased or decreased by 0.01%. This method results in a high statistical likelihood of the identification of the median effective dose (ED50), and has been used to determine the ED50 of many anesthetic medications.

The pre-determined concentration was bupivacaine 0.1% wt / vol for the initial patient in each group. After placement of the epidural catheter at either the L3-4 or L2-3 interspace, the patient would receive 20 mL in 5 mL increments of the study medication. The visual analogue scale (VAS) pain score was evaluated at 30 minutes using a 10 cm line on a blank page with the anchor "no pain" on the left and "worst imaginable pain" on the right. When a patient marked 1 cm or less from the left anchor, this was considered a "success" and a "failure" when the mark was > 1 cm from the left anchor. If the initial dose was a Failure, the patient was offered additional rescue dose of medication of 10 mL 0.125% bupivacaine with 100 μg of fentanyl. If the pain score remained > 1 cm from the left anchor, this was considered an unsuccessful epidural catheter placement, and the patient was recategorized as "Redo".

The concentration of bupivacaine for each subsequent patient was determined by the result of the previous patient: if the patient was categorized as a Success, the concentration of bupivacaine would be reduced by 0.01%, whereas if they were categorized as a Failure the concentration would be increased by 0.01% for the subsequent patient. When the patient was categorized as a Redo, the bupivacaine concentration would remain the same. At 30 minutes, patients were also asked about the presence of any nausea or vomiting, or pruritus during the prior 30 minutes. Hypotension requiring treatment with either a fluid bolus or medication was documented. After the patient completed the 30-minute evaluation, the epidural infusion was initiated as per institution standard, and the study data collection was completed.

The sample size necessary for the adequate determination of the ED50 using the up-down, sequential allocation technique is determined by the number of changes in direction of the graph. A change in direction is found with a success af-

ter a failure or a failure after a success. Approximately seven changes in direction are needed, which generally requires between 20 and 40 subjects to be studied. We chose to enroll 40 patient per group in this study, with a total enrollment of 160 patients.

Statistical Analysis

Data are presented as mean ± standard deviation, median (interquartile range), or number (percent of group), as appropriate. Continuous data are compared using one-way analysis of variance (ANOVA) with post-hoc analysis using the Tukey-Kramer test. Ordinal data are compared using the Kruskal-Wallis test. Fisher's exact test was used to compare incidences. The calculation of MLAC was performed using the technique described by Massey and Dixon, and the medians were confirmed using probit analysis. Statistical significance was determined at the $P \leqslant 0.05$ level. Data were analyzed using NCSS 11 Statistical Software (2016, Kaysville, Utah, USA).

RESULTS

A total of 160 patients completed the study, with 40 in each medication group. Baseline demographic and obstetric characteristics are detailed in Table 1; no differences were identified among the groups. We had only seven (n = 7) patient categorized as Redo, divided among BUP (n = 1), BUP-FEN (n = 3), BUP-EPI (n = 2), and BUP-FEN-EPI (n = 1) (Figure 1, P = 0.66.)

The MLAC of bupivacaine for each group is detailed in Table 2. The addition of epinephrine to either bupivacaine or bupivacaine-fentanyl resulted in a 31% increase in the relative potency of the solution ($P < 0.01$ for both). The addition of fentanyl resulted in a 41% increase in the relative potency of the epidural solution (BUP-FEN vs. BUP, $P < 0.01$). The BUP group had 18 subjects who were categorized as Success with the lowest concentration of successful pain relief being 0.07%; the BUP-EPI group had 20 subjects who were categorized as Success the lowest concentration of successful pain relief being 0.05% bupivacaine; the BUP-FEN group had 19 subjects who were categorized as Success with the lowest concentration of successful pain relief being 0.03%; and the BUP-FEN-EPI group had 23 subjects who were categorized as Success with the lowest concentration of successful pain relief being 0.01%. In fact, two patients in the BUP-FEN-EPI group received 0.01% bupivacaine, with one categorized as a Failure and one as a Success; at the request of the institutional ethics board, we could not administer a solution without bupivacaine and per their request, the subsequent patient received our standard concentration of 0.04% bupivacaine. This concentration was chosen empirically (10). There were no serious complications in any group, and minor side effects were similar among groups (Table 3).

DISCUSSION

We found that the addition of both 1.67 μg/mL of epinephrine or 1.67 μg/mL of fentanyl led to a significant reduction in the amount of bupivacaine required to initiate epidural labor pain relief, with fentanyl being more potent at that dose. The addition of both agents resulted in a further reduction of the required bupivacaine concentration. Interestingly, both epidural solutions in which epinephrine was added led to approximately a 30% reduction in the MLAC of bupivacaine, suggesting that the analgesic effects of epinephrine are at least additive to those of fentanyl. The effect of additive analgesic medications such as fentanyl and epinephrine in reducing the MLAC of bupivacaine have previously been identified. Lyons et al. demonstrated that fentanyl reduces the MLAC of bupivacaine in a dose-dependent manner (4). They found that 2 μg/mL of fentanyl reduced the MLAC of bupivacaine by 31%, which is a smaller effect than we observed (59.7% in the present study). This may be due to the significantly lower MLAC of plain bupivacaine that they found (0.069%). The calculated MLAC of bupivacaine varies considerably from one study to the next, and our result is well within the range that others have identified. Some of the variations in MLAC calculations is likely due to variations in populations that are being studied. Polley et al. demonstrated that the addition of 3.33 μg/mL of epinephrine resulted in a similar 30% reduction in the MLAC of bupivacaine in laboring women (11). We hypothesize that the similarity in the reduction in MLAC of bupivacaine between these results may suggest

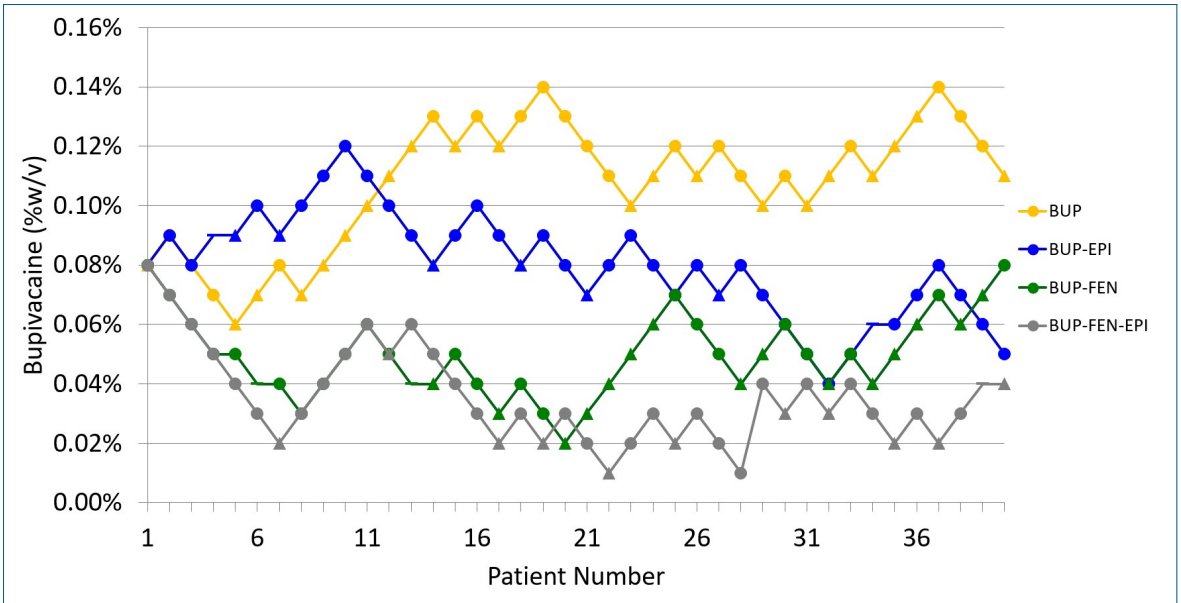

Figure 1. Subject Response to the Administration of 20 mL of Epidural Solution.
Each curve represents the sequential response to the study solution. A solid circle (·) represents a success, denoting that the patient had complete pain relief to the initial dose, solid triangle (Δ) represents a failure, denoting that the patient was not completely pain free (defined as marking > 1 cm on a 10 cm visual analogue line), and a dash (–) represents a redo, denoting that the catheter was unable to produce comfort after additional medications were administered.

Table 2. Calculated Minimum Local Analgesic Concentrations.

Group	Probit	MLAC	95% Confidence Interval	P Value vs. Group Bup
Bup	0.117%	0.119% ± 0.07%	0.15% to 0.09%	--
Bup-Epi	0.063%	0.082% ± 0.05%	0.10% to 0.06%	0.008
Bup-Fen	0.046%	0.048% ± 0.03%	0.06% to 0.04%	< 0.001
Bup-Fen-Epi	0.025%	0.033% ± 0.02%	0.04% to 0.02%	< 0.001

Probit analysis performed with the 50th percentile response (ED50) reported here, minimum local analgesic concentration (MLAC) calculated by the method of Massey and Dixon presented with the standard deviation of the MLAC estimate, and the 95% confidence interval of the MLAC estimate.

Table 3. The Incidence of Side Effects Among Groups.

Side Effect	Group Bup	Group Bup-Fen	Group Bup-Epi	Group Bup-Fen-Epi	P Value
Hypotension	4 (10)	3 (7.5)	1 (2.5)	4 (10)	0.46
Nausea or vomiting	3 (7.5)	3 (7.5)	7 (17.5)	5 (12.5)	0.44
Pruritus	4 (10)	7 (17.5)	3 (7.5)	5 (12.5)	0.56

Comparison made using Fisher's exact test. Data are presented as N (percentage of group).

that we are on the upper plateau of the dose-response curve, and that even lower doses of epinephrine may also be effective.

The pharmacologic mechanism by which epinephrine reduces the required concentration of bupivacaine to produce labor pain relief is difficult to define, but we believe that the reduction of bupivacaine requirements in the initiation of labor pain relief can only be due to the effect of this medication on the alpha-2 adrenergic receptor. The alpha-1 adrenergic mediated vasoconstriction would not affect the initiation of labor analgesia, as this is not impacted by the elimination of medication. Noradrenalin is a potent neurotransmitter involved in pain signaling (13, 14). Activation of the alpha-2 adrenergic recep-

tor in the dorsal horn of the spinal cord has been shown to decrease pain transmission via the wide-dynamic range neurons (15, 16). Furthermore, antagonism of this adrenergic signal has been shown to reverse the analgesia of morphine in an animal model (17). Finally, segmental analgesia has been demonstrated in humans by the epidural administration of both epinephrine and clonidine, which is a more specific agonist for the alpha-2 adrenergic receptor (18).

Not all studies have found the addition of intrathecal epinephrine to be effective. Goodman et al. examined the effect of spinal injections of 35 μg of fentanyl alone or in combination with 2.5 mg of bupivacaine and 100 μg of epinephrine (9). They did not find any additional benefit in pain relief but resulted in higher rates of nausea and motor block from epinephrine. We suspect that their findings may be due to the fairly high doses of spinal medications being used – the effective dose of spinal fentanyl may be as low as 15 μg, or less than half of the dose used in their study (19). The benefit of reducing the concentration of local anesthetic in the epidural solution can be significant. Studies have demonstrated that by using very low concentrations the strength of the lower extremities can be preserved allowing a significant proportion of women to ambulate (10, 20). Furthermore, lower incidences of other side effects such as hypotension and unwanted sensory deprivation have been found clinically when lower concentration epidural solutions are used (5).

Our study has several limitations. Labor pain can have significant variability both among women and throughout the course of labor. Thus, we cannot say that all the women in our study had a similar stimulus which was being treated. This is a common concern in all studies that examine the initiation of labor pain relief and is not unique to ours. Still, it must be considered that a woman who requests epidural pain relief at 3 cm dilation may have different requirements than one who requests pain relief at 5 cm. The use of the up-down sequential allocation method for identifying the median effective dose must be considered with an understanding of the limitations of this technique. This method can identify the median dose effectively but does not describe the dose-response curve of the medication. Thus, while the relative potencies at the median dose are reliable, there may be significant differences at higher, or lower, doses of the various medications. We found that probit analysis confirmed the Massey and Dixon calculation in all of our groups, but there was a decent discrepancy between the ED50 and MLAC in the BUP-EPI group, with probit identifying a concentration that was 25% lower. While this was within the 95% confidence interval of the MLAC calculation, it would be worth confirming the result.

In conclusion, the addition of a small dose of epinephrine to epidural bupivacaine resulted in a 30% reduction in the median effective dose for the initiation of labor pain relief and did not increase the side effects. This effect was seen even with the addition of fentanyl to the epidural solution. The addition of epinephrine to a low concentration epidural solution may allow an even further reduction in the concentration of local anesthetic.

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

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