

Effect of Epidural Epinephrine on the Minimum Local Analgesic Concentration of Epidural Bupivacaine in Labor

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Background: The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration in a 20-ml volume for epidural analgesia in the first stage of labor. The aim of this study was to determine the local anesthetic-sparing efficacy of epidural epinephrine by its effect on the MLAC of bupivacaine.

Methods: In this double-blind, randomized, prospective study, 70 parturients who were at 7 cm or less cervical dilation and who requested epidural analgesia were allocated to one of two groups. After lumbar epidural catheter placement, 20 ml bupivacaine (n = 35) or bupivacaine with epinephrine 1:300,000 (n = 35) was administered. The concentration of bupivacaine was determined by the response of the previous patient in that group to a higher or lower concentration using up-down sequential allocation. Analgesic efficacy was assessed using 100-mm visual analog pain scores, with 10 mm or less within 30 min defined as effective.

Results: The MLAC of bupivacaine alone was 0.091% wt/vol (95% confidence interval, 0.081–0.102). The addition of epinephrine 1:300,000 (66.7 µg) resulted in a significant reduction ($P < 0.01$) in the MLAC of bupivacaine to 0.065% wt/vol (95% confidence interval, 0.047–0.083). The lowest maternal blood pressure was significantly lower in the bupivacaine-epinephrine group ($P = 0.03$). There were statistically significant reductions in fetal heart rate ($P = 0.011$) in the bupivacaine-epinephrine group that were not clinically significant.

Conclusions: The addition of epidural epinephrine 1:300,000 (66 µg) resulted in a significant 29% reduction in the MLAC of bupivacaine. Coincident reductions in fetal heart rate and maternal blood pressure were also observed that were not clinically significant.

WHETHER the addition of epinephrine to local anesthetic solutions used for epidural labor analgesia is advantageous is subject to debate. Previous reports on analgesic and hemodynamic effects have been conflicting. Improvements in both the quality^{1,2} and the duration of analgesia^{1,3-5} have been demonstrated in the parturient. However, other investigations have not found beneficial analgesic effects.⁶⁻⁸ Potential adverse effects include decreased uterine activity,^{9,10} prolongation of labor,^{2,8,11} and increased incidence of motor block.^{7,12}

To evaluate the pharmacodynamic contributions of the various epidural analgesics, we previously described a clinical model to determine the relative potencies of local anesthetic agents in the first stage of labor¹³⁻¹⁵ and to estimate the local anesthetic-sparing potential of epidural opioids.¹⁶⁻¹⁹ The minimum local analgesic concentration (MLAC) has been defined as the median effective local analgesic concentration (EC₅₀) in the first stage of labor. The aim of this study was to determine the local anesthetic-sparing efficacy of epidural epinephrine by its effect on the MLAC of bupivacaine.

Materials and Methods

After institutional review board approval (University of Michigan, Ann Arbor, Michigan) and written informed patient consent were obtained, 70 parturients, classified as American Society of Anesthesiologists physical status I or II, who requested epidural analgesia were enrolled. Participants had singleton pregnancies at greater than 36 weeks' gestation with vertex fetal presentation. All women were in active labor with cervical dilation of 3–7 cm at the time of catheter placement. Those who had received opioid or sedative medication were excluded.

After intravenous prehydration with 1,000 ml of lactated Ringer solution, patients were placed in the flexed sitting position. After raising a midline wheal with 1% wt/vol lidocaine, the epidural space was identified using loss of resistance to saline (2 ml) at the L2-L3 or L3-L4 level, and a multiport epidural catheter was advanced 3 cm into the epidural space. No test dose was used.

Participants were allocated to one of two groups in a double-blind, randomized, prospective study design. Randomization was performed by paired blinded syringes. The first group (n = 35) received 20 ml bupivacaine (Marcaine; Abbott Laboratories, North Chicago, IL) and the second group (n = 35) received 20 ml bupivacaine with 1:300,000 epinephrine (epinephrine injection, Abbott Laboratories). The concentration of bupivacaine received by each patient was determined by the response of the previous patient in that group to a higher or lower concentration using an up-down sequential allocation technique. The testing interval was 0.01% wt/vol. The first patient in each group received 0.07% wt/vol bupivacaine based on an estimate of MLAC from a previous study.¹⁵ Each study solution was freshly prepared by the operating room pharmacist using preservative-free saline as the diluent to achieve the desired concentration at room temperature (20°C). After catheter

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ter placement, patients were placed in the supine position with left uterine displacement and 30° elevation of the head of the bed. The injectate was given incrementally within 5 min. Patients were monitored with a Dinamap (Critikon Inc., Tampa, FL) blood pressure monitor, pulse oximetry, and tococardiography. Hemodynamic data were recorded at 5-min intervals.

The anesthesiologist performing the procedure and subsequent assessment was blinded to the concentration used and group allocation. Efficacy of the study drug was assessed using 100-mm visual analog pain scores (VAPS; where 0 represented “no pain” and 100 was “worst possible pain”) at 10-min intervals for the first 30 min after bolus injection. A VAPS of 10 mm or less was defined as effective. Three outcomes were considered:

1. Effective: VAPS of 10 mm or less during contractions within 30 min of injection. A result defined as effective directed a 0.01% wt/vol decrement for the next patient in that group.
2. Ineffective: VAPS greater than 10 mm as a result of pain that responded to rescue with a 12-ml bolus dose of 0.25% wt/vol bupivacaine. A result defined as ineffective directed a 0.01% wt/vol increment for the next patient in that group.
3. Reject: VAPS greater than 10 mm as a result of pain not responsive to rescue. A result defined as a reject directed a repeat of the same concentration for the next patient in that group.

At 30 min, participants not defined as having effective analgesia were given the rescue bolus dose. Those not responsive to rescue were designated as rejects. Further management then included repeat epidural catheterization, intrathecal opioid with or without bupivacaine, or parenteral opioid as appropriate. Parturients who entered the second stage of labor during the study were also rejected. The onset of second stage was defined as complete cervical dilation.

In addition to VAPS assessment, other data collected at 10-min intervals included sensory level and degree of motor blockade. Sensory level was determined by perceived temperature difference to alcohol swab. Motor block was assessed bilaterally at 15-min intervals using the modified Bromage scale (0 = no motor block; 1 = inability to increase the extended leg, able to move knees and feet; 2 = inability to increase the extended leg and to move knees, able to move feet; and 3 = complete motor block of the lower limbs).

To determine the duration of effective analgesia, women reporting a VAPS 10 mm or less received no additional medication until their request. At that time, the study was complete, and patients were started on an infusion of 0.0625% bupivacaine with 3 µg/ml fentanyl.

Table 1. Demographic and Obstetric Data

	Bupivacaine–Control	Bupivacaine–Epinephrine 1:300,000
Age (yr)	29 (4.1)	30 (5.0)
Height (cm)	164 (6.9)	164 (7.4)
Weight (kg)	82 (11.9)	83 (14.7)
Gestation (weeks)	40 (1.2)	40 (1.0)
Cervical dilatation (cm)	4 [4, 5]	4 [4, 5]
Nulliparous	20	20
Oxytocin	20	18
Initial VAPS (mm)	80 [71, 95]	79 [65, 90]

Results are expressed as mean (SD), median [interquartile range], and count as appropriate.

VAPS = visual analog pain score.

Fetal Assessment

Fetal heart rate was continuously monitored by tococardiography, and any adverse events were recorded. A perinatologist blinded to the study group allocation reviewed fetal heart rate tracings obtained during the first hour of the study and compared them with baseline tracings using the National Institutes of Health research guidelines for interpretation of electronic fetal heart rate monitoring.²⁰

Statistical Analysis

Demographic and obstetric data were collected and are presented as mean (SD), median (interquartile range), and count as appropriate. Mean (SD) values were analyzed using the unpaired Student *t* or Welch *t* tests for differing variances and repeated-measures analysis of variance, medians (interquartile ranges) were analyzed by Mann–Whitney U tests, and counts or proportions were analyzed by Fisher exact tests. The median effective concentrations were estimated from the up–down sequences using the method of independent paired reversals, which enabled MLAC with 95% confidence interval to be derived. The sequences were also subjected to Wilcoxon and Litchfield probit regression analyses as backup or sensitivity tests. Analyses were conducted using the following software: Microsoft Excel 2000 (Microsoft Corp., Redmond, WA), Statistical Package for the Social Sciences 9.0 (SPSS, Inc., Chicago, IL), and GraphPad InStat 3.05 (GraphPad Software, San Diego, CA). Statistical significance was defined for overall α error at the 0.05 level. All *P* values were two-sided. Sample size estimations were based on the SD (SD 0.03% wt/vol) from a previous MLAC bupivacaine study.¹⁵ Power was given at 0.8 to detect a minimum difference of 0.03% wt/vol in the MLAC of bupivacaine as significant (*P* < 0.05). It was then estimated that a minimum of 32 women would be required per group.

Results

There were no significant demographic or obstetric differences between the two groups (table 1). Compar-

Table 2. Maternal and Fetal Hemodynamic Data

	Bupivacaine–Control	Bupivacaine–Epinephrine 1:300,000
Baseline maternal MAP (mmHg)	93 (11.6)	94 (12.9)
Lowest maternal MAP (mmHg)*	84 (9.4)	79 (9.8)
Overall maternal HR (beats/min)	79 (10.9)	82 (12.9)
Overall maternal SpO ₂ %	99 (1.2)	99 (1.1)
Baseline fetal HR (beats/min)	137 (11.9)	133 (9.2)
Overall fetal HR (beats/min)†	140 (10.3)	134 (10.7)
Lowest fetal HR (beats/min)	128 (8.0)	124 (15.2)

Results are expressed as mean (SD).

* $P = 0.03$. † $P = 0.011$.

MAP = mean arterial pressure; HR = heart rate; SpO₂ = oxygen saturation measured by pulse oximetry.

ison of the lowest recorded maternal mean arterial pressure in both groups revealed a significantly lower value in the women in the bupivacaine–epinephrine group (table 2). Only one patient, who received an effective concentration of bupivacaine with epinephrine, required ephedrine for a systolic blood pressure less than 100 mmHg, which also represented a greater than 20% decrease from baseline. Blood pressure was promptly restored with optimization of left uterine displacement, increased intravenous fluid administration, and two 5-mg doses of ephedrine.

Of the 50 women enrolled in the bupivacaine group, 15 were rejected (table 3), leaving 35 for analysis. The sequences of effective and ineffective analgesia are shown in figure 1. The MLAC of bupivacaine in the control group was 0.091% wt/vol (95% confidence interval, 0.081–0.102) using the method of independent paired reversals and was 0.099% wt/vol (95% confidence interval, 0.086–0.113) using probit regression analysis as a backup sensitivity test.

Of the 44 women enrolled in the bupivacaine–epinephrine group, 9 were rejected (table 3), leaving 35 for analysis. The sequences of effective and ineffective analgesia are shown in figure 2. The MLAC of bupivacaine in the bupivacaine–epinephrine group was 0.065% wt/vol (95% con-

Table 3. Distribution of Rejects

Bupivacaine (% wt/vol)	Bupivacaine–Control	Bupivacaine–Epinephrine 1:300,000
0.12	1*, 1†	
0.11	1‡	
0.10		
0.09	2*, 3†, 1§	
0.08	1*, 1†, 1‡, 1§, 1	1*
0.07	1*	1*
0.06		1*, 1‡, 1§
0.05		1‡
0.04		1*, 1†, 1

* Visual analog pain score > 10 mm due to pain which fails to respond to rescue; concentration repeated. † Protocol violation; concentration repeated. ‡ Second stage of labor before study completion; concentration repeated. § Intravascular epidural catheter; concentration repeated. || Patient withdrew from study; concentration repeated.

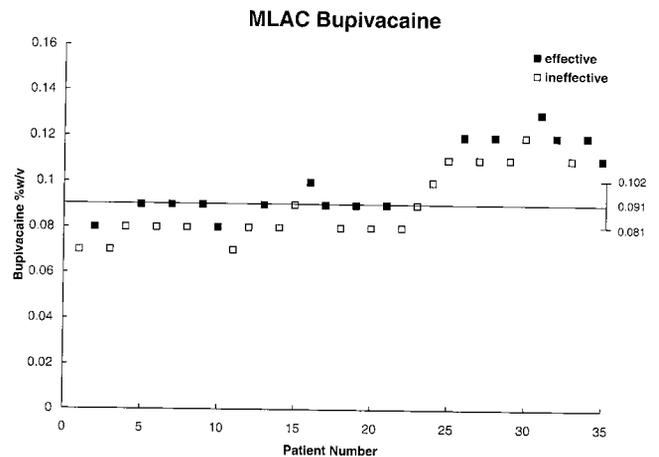


Fig. 1. The median effective local analgesic concentration of bupivacaine as determined by the technique of independent paired reversals. The minimum local analgesic concentration is 0.091% wt/vol. Error bars represent 95% confidence interval. Testing interval was 0.01% wt/vol.

fidence interval, 0.047–0.083) using the method of independent paired reversals and was 0.059% wt/vol (95% confidence interval, 0.040–0.087) using probit regression analysis as a backup sensitivity test.

The addition of epinephrine 1:300,000 resulted in a statistically significant ($P = 0.024$) 29% reduction in the MLAC of bupivacaine.

Block Characteristics

There was no difference between the study groups in the time to onset of the block, which was defined as time to a VAPS 10 mm or less in the effective groups (table 4). There was no difference in the cephalad level of dermatomal spread. Block duration was defined as the time until first patient request for additional analgesia in patients who received effective concentrations of bupiva-

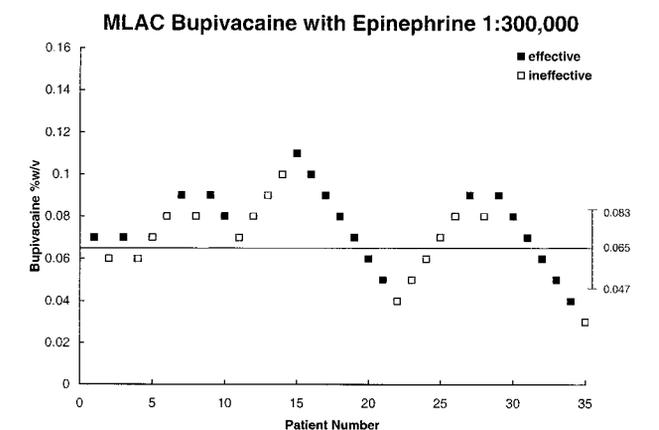


Fig. 2. The median effective local analgesic concentration of bupivacaine with 1:300,000 epidural epinephrine as determined by the technique of independent paired reversals. The minimum local analgesic concentration is 0.065% wt/vol. Error bars represent 95% confidence interval. Testing interval was 0.01% wt/vol.

Table 4. Block Characteristics

	Bupivacaine-Control	Bupivacaine-Epinephrine 1:300,000
Onset time (min)	19 (7.2)	21 (9.1)
Dermatomal level	T9 [T10, T6]	T8 [T10, T7]
Offset time (min)	62 (27.3)	69 (27.2)

Results are expressed as mean (SD) and median [interquartile range].

caine. The addition of epidural epinephrine increased the mean duration of action of the bupivacaine bolus dose by 12%, which was not statistically significant.

Motor Block

There were also no significant differences between the groups in motor block as assessed by the modified Bromage scale. Two parturients in the bupivacaine group and four parturients in the bupivacaine-epinephrine group had a modified Bromage score of 1.

Fetal Assessment

Perinatologist review of continuous fetal heart rate tracings using the National Institutes of Health guidelines did not reveal significant differences between the study groups. No clinical obstetric interventions were performed in response to fetal heart rate. There were no cesarean sections during the study period.

Analysis of the fetal heart rate data recorded at 5-min intervals revealed statistically significant ($P = 0.011$) decreases in fetal heart rate of approximately 10 beats per minute in the bupivacaine-epinephrine group (table 2). These changes were not clinically significant.

Discussion

There has been a steady decline in the concentrations of local anesthetics used for epidural labor analgesia in recent years. Local anesthetic requirements have been reduced with the addition of other epidural analgesics, including opioids and clonidine.^{17-19,21,22} The MLAC model allows for estimation of the epidural analgesic EC_{50} of local anesthetics in the first stage of labor. Using this approach, we were able to quantify the local anesthetic-sparing efficacy of 1:300,000 (66 μ g) epinephrine by its effect on the MLAC of bupivacaine.

Analgesic Effects

Historically, the mechanism for the enhanced and prolonged analgesia observed with the addition of epidural epinephrine was thought to be local vasoconstriction, which limited vascular uptake of local anesthetic in the epidural space.^{6,23} This effect is likely to be less important when the local anesthetic itself has vasoconstrictive properties. Bupivacaine decreases spinal cord and dural blood flow in dogs when administered intrathecally, and epinephrine does not cause further decreases in local

blood flow.²⁴ In humans, the addition of epinephrine to hyperbaric bupivacaine for spinal anesthesia does not reliably prolong the duration of the block.²⁵ More importantly, epinephrine has inherent analgesic properties and produces analgesia even in the absence of local anesthetics,^{26,27} with strong evidence for a spinal α_2 -adrenergic mechanism.²⁸

Previous investigations that failed to find improved quality or duration of analgesia with epidural epinephrine used bupivacaine concentrations of 0.25-0.50% wt/vol.⁶⁻⁸ These studies highlight the difficulty of demonstrating local anesthetic-sparing ability when high concentrations at the top of the analgesic concentration-response curve¹³ are studied. These concentrations correspond to the upper, flatter part of the dose-response curve, where analgesic success is predictable. It is difficult to demonstrate local anesthetic-sparing ability in the presence of supramaximal doses of local anesthetic. Bupivacaine concentrations greater than 0.25% are no longer used routinely for labor analgesia.

Many previous studies focused on prolonged duration of analgesia as a desirable outcome.^{1,3-5,11} With the widespread adoption of the continuous-infusion technique during labor, the duration of single bolus doses is no longer as clinically relevant as in the past. We found that the addition of 1:300,000 epinephrine to epidural bupivacaine increased duration by 12%, which was not statistically significant.

In our study, the addition of epinephrine resulted in a statistically significant 29% reduction in the MLAC of bupivacaine. However, the clinical importance of this may be questioned because much greater reductions have been demonstrated for fentanyl (72%)¹⁶ and sufentanil (91%)¹⁸ coadministered with bupivacaine during labor.

In contrast to the modest augmentation of bupivacaine analgesia found in this study, there is evidence that spinal epinephrine has a profound effect on noxiously evoked activity when administered after spinal fentanyl.²⁷ The MLAC model is well suited to a future investigation of the effects of spinal epinephrine on the EC_{50} of spinal opioids.

Maternal and Fetal Hemodynamic Effects

At one time, it was thought that the addition of epinephrine to local anesthetic solutions might provide "cardiovascular support" to counter the undesirable hemodynamic effects of sympathetic blockade during regional anesthesia. It is now well recognized that peripheral β -adrenergic effects are more important than α -adrenergic effects and result in decreased peripheral resistance and increased heart rate and cardiac output.²⁹ We observed a significant decrease in the lowest recorded maternal mean arterial pressure in the bupivacaine-epinephrine group, consistent with peripheral β -adrenoceptor activation. This finding was of minimal

clinical significance, and only one patient who received an effective concentration of bupivacaine with epinephrine required ephedrine. Other investigators have also observed small decreases in maternal blood pressure with the use of epidural epinephrine.³⁰

Analysis of fetal heart rate recorded intermittently at 5-min intervals during the study revealed a significant reduction in the bupivacaine-epinephrine group of approximately 10 beats per min, although there was no difference between the groups in the lowest fetal heart rate (table 2). This subtle difference did not have any obvious clinical significance. Careful examination of the continuous fetal heart rate tracings by a perinatologist blinded to study group assignment using the National Institutes of Health research guidelines did not reveal any differences between the groups in terms of change in fetal heart rate from preepidural baseline, frequency of fetal heart rate decelerations, contractions per minute, or fetal heart rate variability.

Of more concern, a recent comparison of continuous epidural infusions of bupivacaine *versus* bupivacaine with 40 µg/h epinephrine in laboring women found that fetal pH was significantly lower, although still normal, in the epinephrine group.² The investigators attributed the change in pH to the longer second stage of labor in the study group. At this point in time, the effects of epinephrine on fetal hemodynamic status are not fully understood.

Changes in Uterine Activity

The effects of epinephrine on uterine activity and length of labor also remain controversial. Systemic absorption of epinephrine from the epidural vasculature may result in decreased uterine activity secondary to β-adrenergic stimulation.³¹ This tocolytic effect is secondary to a decrease in the intensity rather than the frequency of uterine contractions¹⁰ and appears to be dose-dependent. It is difficult to directly compare previous investigations because there are multiple methodologic differences, including bupivacaine concentrations, cervical dilation at time of epidural placement, and use of artificial amniotomy and oxytocin. We chose to study a 1:300,000 concentration because it did not alter uterine activity or prolong labor in several investigations,³⁻⁵ whereas a 1:200,000 concentration has been associated with tocolytic effects.^{8,10,11}

Motor Block

There is evidence that epidural epinephrine may increase the incidence of motor block.³² We did not observe any significant differences in motor block using dilute concentrations of bupivacaine and 1:300,000 epinephrine, but there was a trend toward increased motor block (Bromage score 1) in the epinephrine group. Of note, our study examined local anesthetic-sparing after a bolus technique. With a continuous-infusion technique, differences in motor blockade may become more

apparent. One of the most important and relevant reasons for adding pharmacologic agents to local anesthetics for labor analgesia is to reduce the incidence of motor block. Diminution in motor strength is undesirable because it may interfere with maternal expulsive efforts, prolong the second stage of labor, or increase the incidence of instrumental delivery.³¹ Clearly, adjunctive drugs with potential for increased motor blockade have limited clinical utility.

In summary, this study demonstrated a modest local anesthetic-sparing effect of 66 µg epidural epinephrine using the MLAC methodology. Potential disadvantages of epinephrine include tocolytic effects and diminution in motor strength. The effects of epinephrine on the fetus are not fully understood. In light of the relatively weak analgesic efficacy of epidural epinephrine and the unresolved questions regarding side effects, the routine addition of epinephrine to local anesthetic solutions for labor may not offer significant clinical advantage. The principal finding of this study was that addition of 1:300,000 epinephrine (66 µg) resulted in a significant 29% reduction in the MLAC of bupivacaine in the first stage of labor for the parturients in this study.

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