

Effect of Intravenous versus Epidural Fentanyl 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 (EC₅₀) in a 20-ml volume for epidural analgesia in the first stage of labor. The aim of this study was to determine the relative local anesthetic sparing efficacies of intravenous and epidural fentanyl by comparison of their effects on the MLAC of bupivacaine.

Methods: In this double-blind, randomized, prospective study, 84 parturients at ≤ 7-cm cervical dilation who requested epidural analgesia were allocated to one of two groups. After lumbar epidural catheter placement, 20 ml bupivacaine (n = 44) or bupivacaine with 3 µg/ml (60 µg) fentanyl (n = 40) was administered. The plain bupivacaine group then received 60 µg intravenous fentanyl. The bupivacaine-fentanyl group received intravenous saline. 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 within 30 min defined as effective.

Results: The MLAC of bupivacaine-intravenous fentanyl was

0.064% wt/vol (95% confidence interval, 0.049–0.080), and the MLAC of bupivacaine-epidural fentanyl was 0.034% wt/vol (95% confidence interval, 0.017–0.050). Epidural fentanyl significantly increased the analgesic potency of bupivacaine by a factor of 1.88 (95% confidence interval, 1.09–3.67) compared with intravenous fentanyl. The epidural fentanyl group demonstrated significantly higher dermatomal spread (P = 0.0064) and increased pruritus (P = 0.01).

Conclusions: Epidural fentanyl significantly reduced the MLAC of bupivacaine when compared with intravenous fentanyl for the parturients in this study. The significantly enhanced local anesthetic sparing, dermatomal level, and pruritus with epidural fentanyl suggest a primarily spinal site of action. (Key words: Obstetric; pregnancy.)

OPIOIDS are often combined with local anesthetics for epidural administration during labor. Epidural solutions of fentanyl and bupivacaine have been shown to provide superior analgesia to bupivacaine alone with decreased bupivacaine requirements and motor blockade.^{1,2} Motor blockade is undesirable because it may interfere with maternal expulsive efforts, prolonging the second stage of labor or increasing the incidence of instrumental delivery.³

The primary site of action of epidural opioids remains controversial. Analgesia results from the interaction of opioids with multiple opioid receptor systems in brain and spinal cord.⁴ Epidurally administered fentanyl exerts a spinal effect by penetration of the dura, passage through the central nervous system, and entrance into the dorsal horn of the spinal cord to bind with opioid receptors. Epidural fentanyl also may exert a supraspinal or systemic effect. Both systemic absorption from the epidural vasculature and cephalad spread in cerebrospinal fluid would allow for fentanyl interaction with supraspinal receptors. Whether the spinal or supraspinal site is predominantly responsible for fentanyl analgesia is unclear. Investigators of previous studies have reached conflicting conclusions with support for either a primary spinal⁵⁻¹⁰ or primarily supraspinal¹¹⁻¹³ site of action.

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EPIDURAL FENTANYL ACTS PRIMARILY AT SPINAL SITE IN LABOR

To evaluate the pharmacodynamic contributions of various epidural analgesics, a clinical model was devised to determine the relative potencies of local anesthetics in the first stage of labor¹⁴⁻¹⁶ and to estimate the local anesthetic sparing potential of epidural opioids.^{2,17,18} 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 relative efficacies of intravenous and epidural fentanyl by comparison of their effects on the MLAC of bupivacaine.

Materials and Methods

After institutional review board approval and written informed patient consent were obtained, 84 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 lactated Ringer's 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 = 44) received 20 ml of epidural bupivacaine (Marcaine; Abbott Laboratories, North Chicago, IL) immediately followed by 60 µg of intravenous fentanyl (fentanyl citrate; Abbott Laboratories) diluted to a 2-ml volume. The second group received 20 ml of epidural bupivacaine with 3 µg/ml fentanyl immediately followed by 2 ml of intravenous saline. The concentration of local anesthetic received by a particular 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.¹⁶ 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 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 within 5 min. Patients were monitored with a Dinamap (Critikon Inc., Tampa, FL) blood pressure monitor, pulse oximetry, and tococardiography. Measurements were recorded at 10-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 was defined as effective. Three outcomes were considered:

1. Effective: VAPS of ≤ 10 mm 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 due to pain that responded to rescue with a 12-ml bolus 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 due to pain not responsive to rescue. A result defined as a reject directed that the same concentration be repeated for the next patient randomized to that group.

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

To determine the duration of effective analgesia, women reporting a VAPS ≤ 10 mm 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.

In addition to VAPS assessment, other data collected at 10-min intervals included fetal heart rate and maternal blood pressure, heart rate, and oxygen saturation. Sensory level as determined by perceived temperature difference to alcohol swab was also recorded. Pruritus was

assessed by the patient as none (0), mild (1), moderate (2), or severe (3). Request for treatment and treatment received was also recorded.

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 using the National Institutes of Health research guidelines for interpretation of electronic fetal heart rate monitoring.¹⁹

Statistical Analysis

Demographic and obstetric data were collected and are presented as mean (SD), median (interquartile range), and count as appropriate. Means (SD) were analyzed using unpaired Student *t* or Welch *t* tests for differing variances, 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 Dixon and Massey,²⁰ which enabled MLAC with 95% confidence interval (CI) to be derived. The sequences were also subjected to Wilcoxon and Litchfield probit regression analyses as back-up or sensitivity tests. Analyses were performed using the following software; Microsoft Excel 97 (Redmond, WA), Number Cruncher Statistical Systems 2000 (NCSS Inc., Kaysville, UT), GraphPad Instant 3.01 (GraphPad Software, San Diego, CA), and Pharmacological Calculation System 4.2 for DOS. # 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 0.026% wt/vol) from a previous MLAC bupivacaine study.¹⁶ Power was given at 0.8 with a minimum difference of 0.03% wt/vol to be significant. It was then estimated that a minimum of 24 women would be required per group.

Results

There were no significant demographic, obstetric, or hemodynamic differences between the two groups (ta-

Tallarida RJ, Murray RB: Manual of Pharmacologic Calculations with Computer Programs, 2nd edition. New York, Springer-Verlag New York Inc, 1987.

Table 1. Demographic and Obstetric Data

	Bupivacaine— Intravenous Fentanyl	Bupivacaine— Epidural Fentanyl
Age (yr)	29.7 (6.13)	28.1 (3.96)
Height (cm)	163.4 (7.00)	163.1 (7.20)
Weight (kg)	85.2 (17.14)	83.5 (14.53)
Gestation (wk)	39.8 (1.36)	39.9 (1.17)
Cervical dilatation (cm)	4.4 (1.07)	4.7 (1.01)
Nulliparous	8	14
Oxytocin	11	16
Initial VAPS (mm)	81 [68–90]	72 [62–80]

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

VAPS = visual analog pain score.

bles 1 and 2). Maternal hypotension, defined as a systolic blood pressure less than 100 mmHg, which also represented a decrease from baseline mean arterial pressure of more than 15%, did not occur in either study group.

Of the 44 women enrolled in the intravenous fentanyl group, 14 were rejected (table 3), leaving 30 for analysis. The sequences of effective and ineffective analgesia are shown in figure 1. The MLAC of bupivacaine in the intravenous fentanyl group was 0.064% wt/vol (95% CI, 0.049–0.080) using the formula of Dixon and Massey and was 0.062% wt/vol (95% CI, 0.047–0.077) using probit regression analysis as a back-up sensitivity test.

Of the 40 women enrolled in the epidural fentanyl group, 10 were rejected (table 3), leaving 30 for analysis. The sequences of effective and ineffective analgesia are shown in figure 2. The MLAC of bupivacaine in the epidural fentanyl group was 0.034% wt/vol (95% CI, 0.017–0.050) using the formula of Dixon and Massey and was 0.033% wt/vol (95% CI, 0.015–0.050) using probit regression analysis as a back-up sensitivity test.

Epidural fentanyl significantly increased the analgesic potency of epidural bupivacaine by a factor of 1.88 (95% CI, 1.09–3.67) when compared with intravenous fentanyl.

Table 2. Hemodynamic Data

	Bupivacaine— Intravenous Fentanyl	Bupivacaine— Epidural Fentanyl
Baseline MAP (mmHg)	92.9 (8.85)	94.6 (12.57)
Lowest MAP (mmHg)	84.1 (9.57)	85.5 (11.85)
Maternal HR (beats/min)	80.9 (8.83)	81.4 (12.16)
Maternal SpO ₂ %	97.9 (1.41)	97.8 (1.27)
FHR (beats/min)	135.0 (13.69)	133.9 (10.53)

Results are expressed as mean (SD).

MAP = mean arterial pressure; HR = heart rate; FHR = fetal heart rate.

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Table 3. Distribution of Rejects

% wt/vol	Bupivacaine— Intravenous Fentanyl	Bupivacaine— Epidural Fentanyl
0.08	1(A) 1(C)	
0.07	2(B) 2(C)	
0.06	1(A) 1(B)	
0.05	3(A) 1(B) 1(C)	
0.04	1(C)	1(A) 1(C)
0.03		2(A) 1(B)
0.02		1(C)
0.01		1(A) 1(C)
0.00		1(A) 1(C)

A = visual analog pain score greater than 10 mm caused by pain that fails to respond to rescue; B = protocol violation, concentration repeated; C = second stage of labor before study completion, concentration repeated.

Sensory Block

The epidural fentanyl group demonstrated significantly higher dermatomal spread (median T8) than the intravenous fentanyl group (median T10) ($P = 0.0064$). There was no significant difference between the study groups in the time to onset of the block, which was defined as time to a VAPS ≤ 10 mm in the effective groups. There was also no significant difference between the groups in block duration, which was defined as the time until first patient request for additional analgesia in patients who received effective concentrations of bupivacaine (table 4).

Pruritus

Two patients in the intravenous fentanyl group experienced pruritus, which they assessed as mild (1). Eleven

patients in the epidural fentanyl group experienced pruritus: two moderate (2) and nine mild (1) assessments. This difference between the groups was significant ($P = 0.01$). None of the patients requested treatment.

Fetal Assessment

Review of the fetal heart rate tracings 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.

Discussion

In recent years, there has been a steady decline in the concentrations of local anesthetics used for epidural analgesia in labor. Further reduction of local anesthetic concentrations has been possible with the addition of other epidural analgesics, such as opioids and clonidine.^{1,21} Many studies have described and compared various regimens for epidural analgesia. However, it has been difficult to determine the contribution of each drug to the overall efficacy of the analgesia. The anesthetic potencies of volatile agents have been quantified in terms of minimum alveolar concentration, and the same concept can be applied to epidural analgesics. The MLAC model allows for the estimation of the epidural analgesic EC_{50} of local anesthetics in the first stage of labor and also the

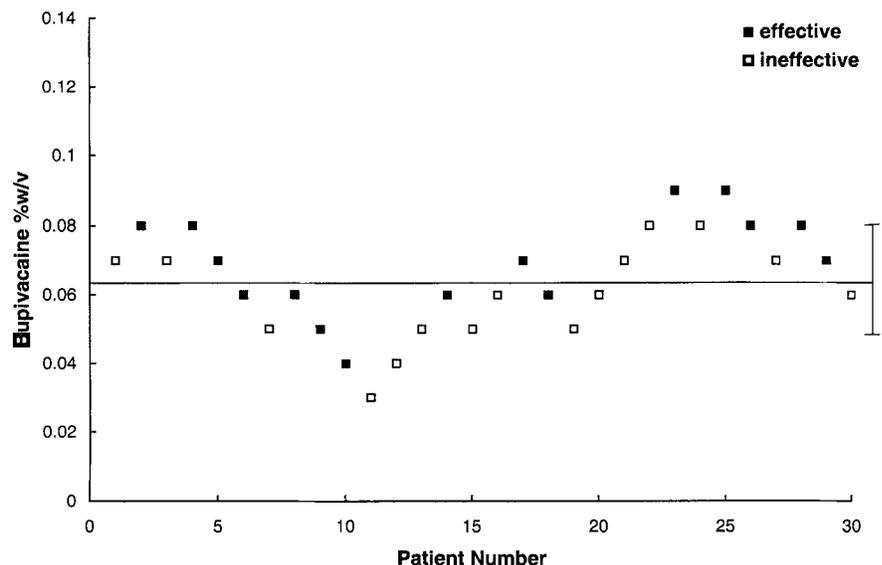
MLAC Bupivacaine (Intravenous Fentanyl 60 μ g)

Fig. 1. The median effective local analgesic concentration of bupivacaine with 60 μ g intravenous fentanyl as determined by the technique of up-down sequential allocation. The minimum local analgesic concentration (MLAC) is 0.064% wt/vol. Error bars represent 95% confidence intervals. Testing interval was 0.01% wt/vol.

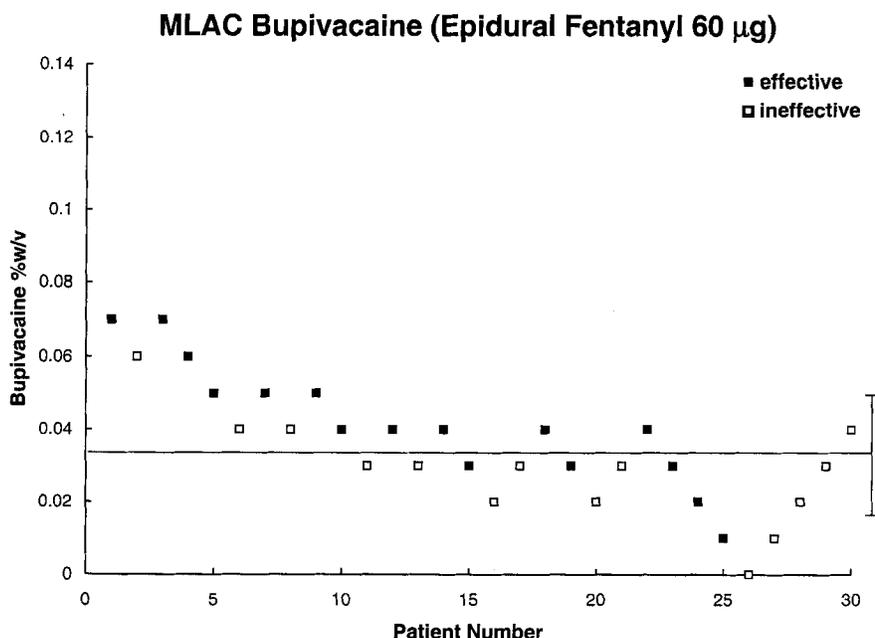


Fig. 2. The median effective local analgesic concentration of bupivacaine with addition of 3 µg/ml (60 µg) epidural fentanyl as determined by the technique of up-down sequential allocation. The minimum local analgesic concentration (MLAC) is 0.034% wt/vol. Error bars represent 95% confidence intervals. Testing interval was 0.01% wt/vol.

effect of the addition of opioids by its effect on the MLAC as the dependent variable. In this study, the model was used to compare the analgesic efficacies of fentanyl given by the intravenous and epidural routes of administration.

Comparison of Intravenous versus Epidural Fentanyl Analgesia

The majority of previous clinical investigations of the site of action of epidural fentanyl have occurred in non-obstetric postoperative patients. In these studies, epidural fentanyl was administered alone (not in addition to a local anesthetic) and compared with intravenous fentanyl. The bolus doses studied for postoperative analgesia ranged from 1 to 4 µg/kg^{6,7,9,11-13,22} and, in some studies, were followed by continuous fentanyl infusions. These dosing regimens exceed the fentanyl doses typi-

cally administered in combination with a local anesthetic to women in labor.

Inagaki *et al.*⁶ studied bolus fentanyl doses of 1, 2, and 4 µg/kg either intravenously or epidurally. In 84 women who underwent hysterectomy, they demonstrated significant reductions in the minimum alveolar concentration of halothane in all epidural fentanyl groups as compared with the same dose in the intravenous fentanyl groups. In the second part of this study, the investigators compared the analgesic effects of the same dosing regimen of epidural and intravenous fentanyl in 70 patients after gastrectomy. Again, epidural fentanyl significantly increased the pressure-pain threshold around the surgical incision at all doses studied. These data suggest that both the anesthetic and analgesic effects of epidural fentanyl, compared with intravenous fentanyl, are mainly due to a spinal effect. Although it has been suggested that the higher fentanyl doses used to treat postoperative pain may mask the spinal effects of epidural fentanyl,¹⁰ there was no evidence of such an effect in this study of multiple doses.

A more recent study examined the effects of lower-dose fentanyl in combination with bupivacaine. Fifty-four laboring women were randomized to receive epidural 0.125% bupivacaine plus one of three treatments: epidural fentanyl (20 µg/h) and intravenous saline, epidural saline and intravenous fentanyl (20 µg/h), or epi-

Table 4. Block Characteristics

	Bupivacaine— Intravenous Fentanyl	Bupivacaine— Epidural Fentanyl
Time to onset (min)	18.7 (7.43)	20.0 (8.17)
Duration (min)	77.0 (27.98)	76.2 (17.17)
Highest dermatomal level*	T10 [T10–T9]	T8 [T9–T8]

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

* $P = 0.0064$ (Mann-Whitney U test).

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dural saline and intravenous saline.¹⁰ Epidural bupivacaine use was patient-controlled and was significantly reduced 28% by epidural fentanyl compared with either intravenous fentanyl or saline placebo.

Conversely, the investigators of several previous postoperative studies concluded that intravenous fentanyl provides equivalent analgesia to epidural fentanyl and that there is no clinical advantage to the epidural route.^{11-13,22,23} However, examination of data collected early in the studies reveals evidence for greater analgesic efficacy with epidural administration. In one investigation,¹¹ three patients in the intravenous group were dropped from the study and analysis in the first 9 h because they failed to achieve pain relief with the highest permitted infusion rate. This represented a significant difference compared with the epidural group. In another study,¹² the mean hourly dose of epidural fentanyl was significantly less compared with the intravenous group during the first 6 h of the study. A third study²³ did not elicit any VAPS data until 18 h postoperatively; therefore, nothing is known regarding earlier relative analgesic efficacy. A possible explanation for these results is that the spinal effects of epidural fentanyl are overwhelmed by systemic or supraspinal effects in the setting of prolonged infusions. Eventually, the supraspinal analgesic effect may predominate.

Diluent volume may also be a salient issue in several studies that failed to find any advantages to the epidural route for fentanyl.^{13,23} It has been demonstrated that diluent volume has a significant effect on the analgesia produced by epidural fentanyl.²⁴ Delivery of 2-ml bolus doses results in poor analgesia with longer time to onset and shorter duration. Participants in studies using 2-ml epidural bolus doses^{13,23} may have received excessive doses of fentanyl to achieve adequate epidural volume for good analgesic effect.

Sensory Level

An interesting finding of this study was the significantly higher dermatomal spread observed in the epidural fentanyl group. This occurred despite the fact that women in the epidural group received less bupivacaine overall than women in the intravenous group. Previous studies have reported higher dermatomal spread of sensory analgesia when intravenous opioids were given in addition to both epidural bupivacaine postoperative analgesia²⁵ and intraoperative lidocaine spinal anesthesia.^{26,27} However, these studies did not make comparisons to epidural opioid administration.

Pruritus

In this study, pruritus was compared after identical bolus doses of intravenous and epidural fentanyl. The significantly increased incidence of pruritus with the epidural route lends further weight to the notion of a predominantly spinal site of action for epidural fentanyl.^{28,29}

Conclusions

This study demonstrated a significant reduction in the MLAC of bupivacaine with epidural fentanyl when compared with intravenous fentanyl administration for the parturients in this study. The significantly enhanced local anesthetic sparing activity, increased dermatomal level, and increased incidence of pruritus that were found with epidural fentanyl suggest a primarily spinal site of action.

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