The Clinical Effectiveness of Epidural Bupivacaine, Bupivacaine with Lidocaine, and Bupivacaine with Fentanyl for Labor Analgesia

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Study Objective: To examine the efficacy of bupivacaine alone and in combination with lidocaine or fentanyl for epidural analgesia during labor.

Design: Randomized, single-blind study.

Setting: Labor and delivery unit at a university medical center.

Patients: Forty-five primiparas requesting epidural analgesia.

Interventions: Following epidural placement at L3–4 interspace, patients received either bupivacaine 0.5% (Group 1, n = 15), bupivacaine 0.25% with lidocaine 1% (Group 2, n = 15), or bupivacaine 0.5% with fentanyl 50 μg in 10 ml of saline (Group 3, n = 15). Patients in Groups 1 and 2 received 6 to 10 ml of local anesthetic depending on patient height, while patients in Group 3 received 5 ml of local anesthetic plus 50 μg of fentanyl in 10 ml of saline. All solutions contained epinephrine 1:200,000.

Measurements and Main Results: Patients were assessed at regular intervals following administration of the epidural solution. Visual analog scale (VAS) scores were used to measure onset of analgesia, time to complete pain relief, duration of analgesia, and patient satisfaction with therapy. The frequency of shivering and pruritus and the extent of sensory/motor block also were evaluated. There were no intragroup differences in time to complete pain relief or patient satisfaction. However, patients in Group 3 noted the most rapid onset and longest duration of pain relief. Patients in Group 3 also experienced significantly less shivering and had the lowest degree of motor block. Two patients in Group 3 experienced mild pruritus.

Conclusions: Epidurally administered fentanyl safely extended the duration of labor analgesia while reducing bupivacaine dose requirements and magnitude of motor block. In this setting, the combination of bupivacaine and lidocaine offered no clinical advantage over bupivacaine alone.

Keywords: Anesthesia, obstetric; analgesia, epidural; local anesthetics, bupivacaine, lidocaine; opioids, fentanyl.
Introduction

The ideal epidural anesthetic for labor and delivery should provide useful analgesia without significant motor block or risk of maternal or fetal toxicity. In this regard, 0.25% to 0.5% concentrations of bupivacaine are commonly used, since they offer effective and prolonged pain relief. While bupivacaine’s prolonged duration of analgesia and lack of immediate or long-term neonatal effects offer advantages in this setting, its slow onset and risk of maternal cardiotoxicity, even in dilute concentrations, represent undesirable characteristics.

A number of pharmacologic adjuncts, including bicarbonate, opioids, epinephrine, and rapid-acting local anesthetics, have been added to solutions of bupivacaine to speed analgesic onset, reduce dose requirements, and lower risks of toxicity. Concomitant administration of bupivacaine and opioid analgesics appears to speed onset and improve the quality of pain relief despite considerable reductions in local anesthetic doses. Reported rapid onset and reduced bupivacaine requirements when epidural combinations of bupivacaine and lidocaine were used for labor and delivery analgesia.

The following randomized, single-blind evaluation studied the clinical effectiveness of epidural anesthesia observed with bupivacaine 0.5% against that provided by combinations of bupivacaine 0.25% and lidocaine 1% and bupivacaine 0.5% and fentanyl. The evaluation measured time of onset and duration of analgesia and determined the relative safety of each solution administered as a single bolus dose in term parturients in Stage I of active labor.

Materials and Methods

The study was approved by the Yale University School of Medicine Human Investigation Committee, and informed consent was obtained from all patients prior to epidural placement. Forty-five term primiparas in active labor (at 3 to 6 cm cervical dilation) requesting epidural analgesia were randomly assigned to one of three treatment groups. Patients selected were healthy (ASA physical status II), had uncomplicated pregnancies with a singleton fetus in vertex position, had not received parenteral analgesics or sedatives, were at least 18 but no more than 40 years of age, weighed no more than 110 kg, and were at least 152 cm but no more than 183 cm in height. Patients with a history of alcohol or drug abuse or a documented sensitivity to opioids or local anesthetics were excluded from the study.

Following prehydration with lactated Ringer’s solution (15 ml/kg) and routine epidural placement at the L3–4 interspace, patients received one of three test solutions via a 19-gauge single-port epidural catheter (Kendall Curry, Mansfield, MA) inserted 9 cm in randomized, single-blind fashion. Patients in Group 1 (bupivacaine, n = 15) received 5 ml of 0.5% bupivacaine plus epinephrine 1:200,000 followed by additional bolus doses based on height (per standard routine, patients 152 cm tall received an additional 1 ml, those 160 cm tall received 3 ml, and those 170 cm and taller received 5 ml). Patients in Group 2 (bupivacaine with lidocaine, n = 15) received a 5 ml mixture of 0.25% bupivacaine plus 1.0% lidocaine plus epinephrine 1:200,000, followed by additional 1 to 5 ml doses as outlined for Group 1. Patients in Group 3 (bupivacaine with fentanyl, n = 15) were given 5 ml of 0.5% bupivacaine plus epinephrine 1:200,000, followed by 50 μg of fentanyl plus 9 ml of 0.9% sterile saline. All patients remaining uncomfortable 15 minutes after epidural administration were given supplemental 1 to 2 ml boluses of their respective study solution as required. Epidural catheters were rechecked in all patients remaining uncomfortable after 30 minutes. If a catheter was found to be misplaced, the individual was dropped from evaluation and a second epidural was inserted. All medication was administered in divided doses with patients supine and in left uterine displacement. Patients were monitored continuously with electrocardiogram (ECG) and automated sphygmomanometer cuff.

A blinded obstetric anesthesiologist collected data prior to epidural placement (baseline), every 5 minutes for the first 30 minutes following drug administration, and then every 30 minutes until epidural reinforcement was requested. At each data collection interval, a 10 cm VAS (anchored with 0 representing no pain and 10 representing the worst possible pain) was used to assess analgesic onset, duration, and quality of pain relief. A similar VAS was used to assess patient satisfaction with therapy, with 0 representing least satisfaction and 10 reflecting most satisfaction. Onset time represented the interval between drug administration and the first VAS score lower than baseline. Duration was defined as the interval from onset of analgesia until the patient requested epidural reinforcement.

The extent of dermatomal sensory block to pinprick and cold (alcohol swab) and the magnitude of motor block were assessed at each data collection interval, immediately following completion of VAS scores. Motor blockade was tested by using a modification of Bromage’s scale, in which 0 = the ability to maintain a leg lift for prolonged periods; 1 = the
ability to lift legs briefly, 2 = the ability to bend knees, 3 = the ability to wiggle toes; and 4 = no movement in lower extremities.

Maternal side effects, including nausea, pruritus, and shivering, were scored as 0 = absent, 1 = mild, 2 = moderate; and 3 = severe. The blinded observer also noted whether patients were started on intravenous (IV) oxytocin following epidural placement, the frequency of fetal bradycardia [heart rate (HR) less than 110 beats per minute (bpm)], maternal hypotension [systolic blood pressure (SBP) less than 100 mmHg], the need to administer ephedrine (as per standard routine, a decrease in SBP below 100 mmHg mandated administration of 5 mg of ephedrine), and total ephedrine dose requirement.

Data were analyzed as follows: patient demographics and continuous variables, including VAS scores and times, were analyzed by analysis of variance (ANOVA) and compared with Tukey's test of multiple comparison; differences in frequency of side effects were analyzed with chi-square tests. Data are expressed as means ± SD, median, or percentage. A value of $p < 0.05$ was considered to be significant.

**Table 1.** Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>27.7 ± 6.7</td>
<td>28.7 ± 5.0</td>
<td>27.7 ± 7.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.2 ± 5.8</td>
<td>164.8 ± 6.8</td>
<td>159.0 ± 4.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.9 ± 18.3</td>
<td>93.6 ± 22.9</td>
<td>79.2 ± 12.9</td>
</tr>
<tr>
<td>Cervical dilation (cm)</td>
<td>5.3 ± 1.6</td>
<td>5.0 ± 1.3</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>Prehydration (ml)</td>
<td>1,423 ± 252</td>
<td>1,515 ± 288</td>
<td>1,390 ± 277</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>123.7 ± 12.2</td>
<td>122.3 ± 11.7</td>
<td>121.7 ± 9.9</td>
</tr>
<tr>
<td>Baseline pain VAS (cm)*</td>
<td>9.0 (7.5 to 10.0)</td>
<td>8.4 (6.0 to 10.0)</td>
<td>8.7 (7.2 to 10.0)</td>
</tr>
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Percentage of patients receiving oxytocin

4 to 6 µg/h 38 27 35

Note: Data are means ± SD.

*Values are medians with range in parentheses.

**Table 2.** Pain and Satisfaction Visual Analog Scale (VAS) Scores

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
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<tbody>
<tr>
<td>Time to onset (min)</td>
<td>10.6 ± 4.9†</td>
<td>8.2 ± 3.9</td>
<td>5.1 ± 1.6</td>
</tr>
<tr>
<td>Time to lowest pain VAS score (min)</td>
<td>14.9 ± 8.3</td>
<td>14.2 ± 10.6</td>
<td>13.6 ± 5.9</td>
</tr>
<tr>
<td>Lowest pain VAS score (cm)*</td>
<td>0.0 (0 to 0.3)</td>
<td>0.2 (0 to 0.6)</td>
<td>0.0 (0 to 0.3)</td>
</tr>
<tr>
<td>Time to highest satisfaction VAS score (min)</td>
<td>15.4 ± 9.2</td>
<td>13.4 ± 11.0</td>
<td>14.0 ± 5.8</td>
</tr>
<tr>
<td>Highest satisfaction* VAS score (cm)</td>
<td>10.0 (9.8 to 10)</td>
<td>9.9 (9.2 to 10)</td>
<td>9.9 (9.6 to 10)</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>116.9 ± 19.6</td>
<td>126.3 ± 32.9</td>
<td>165.1 ± 25.4‡</td>
</tr>
</tbody>
</table>

Note: Data are means ± SD.

*Values are medians with range in parentheses.

†Significant difference Group 1 vs Group 3, $p < 0.05$

‡Significant difference Groups 1 and 2 vs Group 3, $p < 0.05$.

**Results**

All patients included in the present evaluation completed the study protocol—i.e., there were no dropouts secondary to inadequate analgesia, maternal or fetal morbidity, precipitous delivery, or emergency cesarean section. There were no significant differences among the three treatment groups with respect to patient demographics, cervical dilation at placement of epidural analgesia, SBP, volume of lactated Ringer's solution infused prior to epidural placement, or percentage of patients treated with oxytocin (Pitocin) (Table 1).

Pain scores are presented in Tables 1 and 2. There were no significant differences among the three treatment groups with respect to baseline VAS pain score and lowest pain score achieved following administration of the study solutions. Patients in all the treatment groups eventually attained very low pain scores (<1), however, individuals in Groups 1 and 2 required more supplemental boluses and a greater amount of local anesthetic than did those in Group 3 (Table 3). Patients in Group 1 experienced delayed analgesic onset when
compared with individuals in Group 3. However, there were no significant intergroup differences in time required to achieve lowest VAS score (Table 2).

There were no intergroup differences in satisfaction or time necessary to achieve the highest satisfaction score (Table 2). Duration of analgesia was significantly longer in Group 3 than in Groups 1 and 2.

Patients in Group 3 had a significantly lower degree of motor block than those in Groups 1 and 2 (Table 3). There were no intergroup differences in sensory block to pinprick or cold temperature (Table 3).

Following administration of epidural study solutions, more episodes of maternal hypotension occurred in Group 2 than in the other two groups (Table 3). Patients in Group 2 required significantly more IV ephedrine to maintain SBP above 100 mmHg, while those in Group 3 required the least (Group 2 vs Group 3). No episodes of fetal bradycardia or arrhythmia or need for emergency cesarean delivery occurred.

With regard to other adverse events, patients in Group 3 had a significantly lower frequency and severity of shivering than individuals in Groups 1 and 2 (Table 3). There were no episodes of increased maternal sedation and no intergroup differences in sedation scores. Mild abdominal pruritus, which did not require treatment, was noted in two patients in Group 3.

Discussion

The goal of epidural analgesia for labor is to provide rapid and reliable pain relief with minimal maternal or fetal side effects. In this regard, the epidural solutions used in the present investigation offered uniformly excellent analgesia and high patient satisfaction. This single-bolus-dose study did not evaluate neonatal outcome or mode of delivery, since analgesic techniques following termination of the evaluation period were varied and individualized to patient status. While it is recognized that concentrations and total milligrams of local anesthetic administered are higher than amounts reported to provide useful labor analgesia,12,14 dosages represent standard of care at this institution in otherwise unmedicated primiparas. Although there were no intergroup differences in time until peak analgesia, defined as the lowest VAS pain score, or in patient satisfaction with therapy, individuals treated with bupivacaine and fentanyl experienced rapid onset, the longest duration of pain relief, the lowest degree of shivering, and the least motor block. The mixture of bupivacaine and lidocaine offered little clinical advantage in this setting.

A number of clinical studies have documented the effectiveness and safety of epidurally administered fentanyl.4,7 This highly lipid-soluble μ-agonist rapidly crosses dura, activates spinal opioid receptors in dorsal horn, and selectively suppresses c-fiber mediated nociceptive input.15 While not effective by itself,16,17 it appears to potentiate the activity of epidurally administered local anesthetics and improves both the quality and duration of labor analgesia. Onset of analgesia was particularly rapid in patients receiving fentanyl. This finding may reflect rapid systemic uptake and initial supraspinal effects in addition to spinal cord–mediated activity.7 Supraspinal analgesia is of short duration and provides negligible benefit after
20 minutes,\textsuperscript{17} whereas more profound spinal modulation of pain peaks at 10 to 15 minutes and is maintained for 2 or more hours.\textsuperscript{6,7,16} In this regard, patients receiving bupivacaine with fentanyl experienced reductions in pain at the first observation interval (5 minutes); however, analgesia was incomplete, and time to lowest pain score was no more rapid than that observed in the two nonopioid treatment groups.

The duration of pain relief in the bupivacaine with fentanyl group was longer than that recently reported by Lirzin \textit{et al.}\textsuperscript{18} Patients in that study, however, were evaluated at a later stage of labor. It is also recognized that duration of epidural fentanyl analgesia may be increased when administered in larger volumes of solution.\textsuperscript{10} Increasing the volume of epidural injectate is believed to provide greater dispersion in the epidural space and to allow a larger number of fentanyl molecules to reach opiate receptors concentrated in the thoracic/lumbar spinal cord. The relatively large volume of epidurally administered fentanyl solution appeared to dilute the activity of bupivacaine and influenced its localization in that gross motor function was virtually unaffected, while sensory blockade to temperature tended to spread to higher dermatomal levels. As in previous evaluations,\textsuperscript{7,10} this higher dermatomal block was imperceptible to the patient, did not influence sympathetic tone, and was not associated with a higher frequency of hypotension or need for vasopressors. It is unclear whether dilution and greater epidural dispersion would have influenced the onset, duration, and effectiveness of analgesia provided by bupivacaine and bupivacaine with lidocaine. It is conceivable that greater dispersion would have reduced the magnitude of motor blockade.

Solutions of lidocaine are commonly used for epidural analgesia in obstetrics because they provide rapid onset of pain relief with minimal effects on uterine tone\textsuperscript{26} and neonatal outcome.\textsuperscript{24} In contrast to the findings by MaGee \textit{et al.},\textsuperscript{11} the combination of bupivacaine and lidocaine in the present study offered no clinical advantage over bupivacaine alone in terms of onset, duration of analgesia, or degree of motor block and shivering. Duration of analgesia in this group was significantly shorter than that noted with bupivacaine and fentanyl. These findings reinforce the contention that combinations of local anesthetics with different pharmacodynamics offer no clinical advantage over therapeutic doses of the individual agents used.\textsuperscript{8,10}

Perhaps the only advantage to patients in this group was a bupivacaine-sparing effect in which equivalent quality of analgesia and overall patient satisfaction were achieved with significant reductions in total bupivacaine dosage. This finding mirrored a similar reduction observed in the bupivacaine with fentanyl group. It remains unclear whether reductions in bupivacaine dosage improve patient safety by lowering risks of cardiotoxicity.\textsuperscript{19}

In the present study, patients receiving bupivacaine and lidocaine tended to require a greater amount of ephedrine to maintain SBP above 100 mmHg. However, transient episodes of hypotension and IV doses of vasopressor did not influence fetal HR or variability. Few other maternal adverse events were noted in any of the study groups. Patients receiving bupivacaine with fentanyl had a lower frequency of shivering and a higher frequency of mild pruritus than did individuals in the two other treatment groups. Epidural opioids previously have been shown to reduce maternal shivering associated with lumbar epidural analgesia.\textsuperscript{23} Whether this effect represents a supraspinal mode of action or direct inhibition of spinal reflexes remains unclear. Pruritus is a well-documented side effect associated with epidural opioids. As in previous evaluations of epidural fentanyl,\textsuperscript{12,16} this effect was of mild severity and isolated to the abdomen. The frequency of fentanyl-induced pruritus may be directly related to the volume of solution administered rather than the total dose.\textsuperscript{17}

Finally, while patients treated with bupivacaine and fentanyl noted prolonged analgesia, an absence of shivering, and an intact ability to move and adjust body position, such desirable characteristics did not improve overall patient satisfaction. Thus, while patient satisfaction with therapy may reflect the composite of useful analgesia with minimal adverse effects, patients experiencing complete relief of labor pain appear to overlook any associated inconveniences.

In conclusion, solutions of bupivacaine alone and in combination with a second local anesthetic or opioid provided useful epidural analgesia in laboring parturients. The combination of bupivacaine and fentanyl offered the longest duration of analgesia and the lowest frequency of shivering and motor block. The combination of bupivacaine and lidocaine offered little clinical advantage over bupivacaine alone.

References

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