A Randomized Control Trial of Bupivacaine and Fentanyl versus Fentanyl-only for Epidural Analgesia during the Second Stage of Labor

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ABSTRACT

Background: The purpose of this prospective, double-blinded, parallel-arm, randomized trial was to examine the effects of epidural bupivacaine on the length of the second stage of labor in nulliparous women.

Methods: The authors assessed length of second-stage labor, degree of motor blockade, mode of delivery, and visual analog scores in 310 nulliparous women with labor epidurals randomized to receive either: (1) 0.125% bupivacaine and fentanyl 2 μg/ml or (2) fentanyl 10 μg/ml alone via epidural using double blinding.

Results: The median duration of the second stage was 75 min (41, 128) in the bupivacaine/fentanyl group versus 73 min (42, 120) in the fentanyl-only group ($P = 0.17$) with a median difference of 6.0 (95% CI, −6.0 to 18.0). Furthermore, there was no difference in degree of motor blockade, incidence of operative delivery, visual analog scores, or neonatal outcomes between the two groups. No adverse events were reported.

Conclusions: Use of epidural bupivacaine/fentanyl or a fentanyl-only infusion during the second stage of labor did not affect the duration of the second stage of labor, degree of motor blockade, mode of delivery, pain relief, and maternal or neonatal outcomes. However, in the fentanyl-only infusion group, there was a fivefold increase in opioid exposure to the fetus with unknown effects on neurobehavior, an outcome not assessed beyond the immediate postnatal period in this study.

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Institutional Review Board, Dallas, Texas, registered with ClinicalTrials.gov (NCT01621230), and designed to assess the superiority of epidural fentanyl-only versus bupivacaine and fentanyl on the length of second stage of labor. This study was monitored by a Safety and Data Monitoring Board.

All women presenting for labor induction at Parkland Hospital, Monday through Friday, were screened for inclusion in the study. The labor and delivery unit is a closed staff unit; therefore, protocols derived from “labor and delivery,” described in Williams Obstetrics Section 4, were used by the obstetrical service reducing potential bias in management. During labor, eligible women who had an existing epidural were approached for participation and research staff obtained informed written consent. Three hundred ten nuliparous women at term (≥37 weeks), in active labor and with an existing, functional labor epidural in place were enrolled into the study. The primary outcome was the length of the second stage of labor. Secondary outcomes of interest were motor strength score, mode of delivery, intravenous meperidine bolus requirements, satisfaction with pain relief, and indices of maternal and neonatal well-being.

Methods
During the study period, labor and delivery at Parkland Hospital was staffed with a protocol-driven dedicated obstetrical anesthesia service to ensure minimal variation in practice. Epidural analgesia was achieved via placement of an epidural catheter, subsequent 3 ml of 1.5% lidocaine with epinephrine 1:200,000 as test dose solution for possible intravascular or intrathecal placement, followed by 0.25% bupivacaine and 100 μg of fentanyl as the initial bolus using our standard continuous epidural kit (B. Braun Medical Inc., Bethlehem, PA). The initial bolus was then followed with the standard epidural solution used at our institution, 0.125% bupivacaine with 2 μg/ml fentanyl, infused at 10 ml/h. Anesthesia providers were notified by the nurse of patients reporting a visual analog score (VAS) of greater than 2 for assessment and possible intervention. If needed, additional local anesthetic epidural boluses consisting of either bupivacaine 0.25% (typically), bupivacaine 0.5%, and/or lidocaine 2% with epinephrine 1:200,000 were given per the anesthesia provider. If these epidural boluses were determined to be inadequate for pain relief, all participants could receive 25 mg of intravenous meperidine every hour. These boluses were in addition to patient-controlled epidural analgesia demand boluses that were programmed to deliver 5 ml of the study drug every 30 min once enrolled into the study.

Routine cervical examinations were performed approximately every 2 h and randomization occurred at any point between 8 and 10 cm cervical dilation, with subsequent infusion of either our standard epidural solution of 0.125% bupivacaine with 2 μg/ml of fentanyl or epidural fentanyl-only (10 μg/ml concentration). In both groups, infusion rates were started at 10 ml/h. Infusions were prepared by Parkland’s Investigational Drug Services Pharmacy in identical, unlabeled cartridges as part of the blinding effort.

Data Collection
Research personnel performed motor strength assessments (table 1), as well as VAS at randomization, 10 cm cervical dilation, and every 30 min thereafter until delivery. According to the motor strength scale, a score of 5 indicates no weakness in hip flexion. To assess this variable, subjects were asked to flex their knees and lift buttocks off of the bed without assistance. VAS was measured on a linear scale from 0 to 10 (0 = no pain; 10 = worst possible pain). Epidural analgesia was provided per study protocol until either spontaneous delivery of the neonate or operative vaginal delivery or cesarean birth was planned. At this point, the study was terminated and routine anesthesia care resumed.

Women were asked within approximately 1 h after delivery if they were satisfied with their analgesia and if they would choose to have the same form of analgesia with subsequent deliveries. In addition, breastfeeding status of the parturient was also assessed upon discharge. All data were abstracted by research staff using study-specific forms.

Statistical Analysis
The sample size for this study was determined using historical data from Parkland Hospital. Randomization was performed in permuted blocks with computer-generated 1:1 allocation sequence. Epidural infusion cassettes were sequentially numbered. The baseline rate for the primary outcome and the length of second stage were estimated for women with singleton, term gestation pregnancies, requiring labor induction, and without labor epidural analgesia. The median (first and third quartile) lengths of the second stage of labor were estimated at 28 min (15, 58) in women without epidural analgesia. Assuming a one-third increase in the length of the second stage to 37 min due to epidural bupivacaine, a sample size of 155 per arm (310 total) was required for 80% power to detect such a difference using a two-sided Wilcoxon rank sum test. Length of second stage was analyzed using Wilcoxon rank

Table 1. Motor Strength Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unable to move feet or knees (complete block)</td>
</tr>
<tr>
<td>2</td>
<td>Able to move feet only</td>
</tr>
<tr>
<td>3</td>
<td>Able to move knees</td>
</tr>
<tr>
<td>4</td>
<td>Detectable weakness of hip flexion while supine</td>
</tr>
<tr>
<td>5</td>
<td>Ability to flex knees and lift buttock off bed (detection of hip flexion)</td>
</tr>
<tr>
<td>6</td>
<td>Able to perform partial knee bend</td>
</tr>
</tbody>
</table>

Adapted from modified Bromage description of degree of motor blockade (Reproduced, with permission, from Breen TW et al. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg 1993; 77:919-24). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
sum test. Motor strength and VAS were analyzed using a mixed-effect model to estimate the mean (±SEM) under the construct of repeated observations per subject. No assumptions were made restricting the estimation of the covariance structure. Treatment assignment was assumed to be a fixed effect and time, a random effect, accounting for the incompleteness of observations over time. The reported \( P \) values were Tukey–Kramer adjusted for multiple testing of these pairwise comparisons. The remaining outcomes are categorical and were analyzed using Pearson chi-square test. Analysis of results was performed using intent-to-treat in all subjects. Statistical significance was accepted with a \( P \) value of less than 0.05 (SAS version 9.2; SAS Institute, Inc., Cary, NC).

### Results

Between September 7, 2009 and July 16, 2012, a total of 1,013 women met inclusion criteria for this study, 481 (48%) were consented and 310 (64%) were randomized (fig. 1). A total of 171 women were not randomized due to cesarean birth before reaching 8 to 10 cm cervical dilation or precipitous delivery. One hundred fifty-four women were allocated to standard epidural infusion of 0.125% bupivacaine with 2 \( \mu \)g/ml fentanyl and 156 women were allocated to infusion of fentanyl-only (10 \( \mu \)g/ml). As shown in table 2, there were no statistically significant differences in maternal demographics or antepartum complications between the two study groups. The time from randomization to delivery was similar as well, 169 min in the bupivacaine/fentanyl arm and 149 min in the fentanyl-only arm (\( P = 0.29 \)).

### Table 2. Maternal Demographic Characteristics and Antepartum Complications in Women Randomized to Bupivacaine vs. No Bupivacaine during the Second Stage of Labor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bupivacaine (N = 154)</th>
<th>No Bupivacaine (N = 156)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤16</td>
<td>9 (6)</td>
<td>7 (4)</td>
<td>0.59</td>
</tr>
<tr>
<td>≥35</td>
<td>7 (5)</td>
<td>8 (5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.6 ± 5.4</td>
<td>22.9 ± 5.0</td>
<td>0.64</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Black</td>
<td>14 (9)</td>
<td>16 (10)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>133 (86)</td>
<td>133 (85)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (4)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>31.6 ± 7.2</td>
<td>32.1 ± 6.0</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (31)</td>
<td>36 (23)</td>
<td>0.13</td>
</tr>
<tr>
<td>Postterm</td>
<td>9 (6)</td>
<td>11 (7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Ruptured membranes, not in labor</td>
<td>51 (33)</td>
<td>46 (29)</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (6)</td>
<td>11 (7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Randomization to delivery (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>169 (93, 243)</td>
<td>149 (100, 221)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>198 ± 155</td>
<td>180 ± 143</td>
<td>0.27</td>
</tr>
</tbody>
</table>

All data are shown as frequency (percent) unless otherwise annotated in the table. BMI = body mass index.

### Duration of the Second Stage of Labor

The median duration of the second stage was 75 min (41, 128) in the bupivacaine/fentanyl group versus 73 min (42, 120) in the fentanyl-only group (\( P = 0.17 \)) with a median difference of 6.0 min (95% CI, –6.0 to 18.0) (fig. 2).

### Motor Blockade

Motor strength scores were not different between the two study groups with a narrow range suggesting that neither group had a dense motor block. Figure 3 illustrates the distribution of scores over the measured time points.

### Mode of Delivery

There was no difference in the rates of spontaneous delivery (\( P = 0.09 \)), forceps-assisted delivery (\( P = 0.17 \)), or cesarean delivery (\( P = 0.38 \)) between the two study groups (table 3). A subset analysis did reveal a possible association between a low motor strength score and forceps delivery (\( P = 0.02 \)). This seems plausible because in patients with a dense motor block, the second stage was artificially shortened by instrumental vaginal delivery; however, being a secondary analysis, this finding is hypothesis generating and requires further investigation.

### Relief of Labor Pain

Visual analog scores were similar between the two groups with scores ranging from 0 to 7 with a median score between...
and 2 throughout the second stage. Figure 4 illustrates the distribution of scores over measured time points.

There was a small but significant difference in the number of intravenous meperidine boluses given during the second stage. Specifically, the bupivacaine/fentanyl group received an average of 1.2 boluses versus 1.9 in the fentanyl-only group (P = 0.004). However, the amount of meperidine did not differ significantly between the two groups, 0.32 ± 1.20 mg and 0.35 ± 1.12 mg, respectively (P = 0.45). Notably, the total amount of opioid (in morphine equivalents) administered in the second stage was statistically significant, 7.62 ± 6.10 mg in the bupivacaine/fentanyl group and 35.95 ± 25.22 mg in the fentanyl-only group (P ≤ 0.001).

Maternal and Neonatal Well-being
Similarly, the rates of chorioamnionitis (defined as maternal fever 100.4°F [38°C] in labor) did not differ between the study groups (P = 0.48). As shown in table 4, there were no differences in neonatal outcomes with regards to 1- and 5-min Apgar scores (P = 0.55 and 0.57, respectively), umbilical artery pH (P = 0.12), administration of naloxone (P = 0.31), admission to intensive care unit (P = 0.66), or breastfeeding at discharge (P = 0.65).

Discussion
Historically, when high concentrations of local anesthetic were used in labor epidural infusions, motor blockade was significant during the second stage of labor and often resulted in epidural infusions being turned down or completely off to improve maternal expulsive efforts.11 We highlight three clinical observations from our study of paramount interest and importance that address the aforementioned practices.

First, lower-dose epidural bupivacaine infusions such as that used in this trial moderately impeded lower extremity motor function during childbirth. In fact, all women were able to lift their legs against gravity (motor strength score: 3 or higher), further indication that no woman had an extensive motor block. This counters a previously described theory of epidural local anesthetics resulting in poor maternal expulsive efforts, thought to be a cause of increased operative deliveries.12

Second, several investigators have reported that a major disadvantage to lowering or discontinuing the epidural infusion during the second stage of labor is the potential for inadequate analgesia.13–16 In two separate studies, Chestnut et al.13,14 randomized women to either bupivacaine-containing solutions or placebo infusion of saline during the second stage. Women randomized to the saline groups reported higher pain scores. Alternatively, Lindow et al.16 infused epidural opioid in lieu of saline in comparison with epidural bupivacaine/fentanyl. Again, results were similar with women reporting higher pain scores and a greater need for

Table 3. Mode of Delivery in Women Randomized to Bupivacaine vs. No Bupivacaine during the Second Stage of Labor

<table>
<thead>
<tr>
<th>Mode of Delivery</th>
<th>Bupivacaine</th>
<th>No Bupivacaine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>112 (73)</td>
<td>126 (81)</td>
<td>0.09</td>
</tr>
<tr>
<td>Forceps-assisted</td>
<td>19 (12)</td>
<td>12 (8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cesarean</td>
<td>23 (15)</td>
<td>18 (12)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

All data are shown as frequency (percent).

Fig. 2. Duration of the second stage of labor in respective groups.

Fig. 3. Distribution of motor strength scores over measured time points in respective groups.

Fig. 4. Distribution of visual analog scores over measured time points in respective groups.
“rescue” analgesia of nitrous oxide and/or perineal infiltration of lidocaine in the fentanyl-only group. Of note, these studies had sample sizes of less than 100 women.

A meta-analysis was performed analyzing the possible consequences of discontinuing epidural analgesia late in labor.17 The only significant finding was an increase in pain. In contrast, our study found that pain scores were equally satisfactory among both groups. This is likely due to the higher concentration of fentanyl (10 μg/ml) used in our study versus saline and a fentanyl concentration of 1.6 μg/ml used in the study by Lindow et al.16

Last, substituting epidural bupivacaine with fentanyl-only (10 μg/ml) during the second stage of labor was not associated with deleterious maternal or neonatal effects. Although there was a negligible amount of intravenous meperidine given in both study arms, epidural fentanyl administration was five times greater in the fentanyl-only group. This increase in fetal opioid exposure is because epidural fentanyl is rapidly absorbed systemically. Although the bioavailability is unknown in laboring women, transplacental transfer is approximately 90%.18

We report three limitations to our study. First, to estimate sample size, from our database, we included women of parity 0 and 1, which would explain the shorter median duration of the second stage at 28 min (15, 58) than what was observed in this study. Our study consisted of all nulliparous women. Second, having a third arm, with subjects that had a placebo infusion started after randomization, would have allowed us to evaluate the effects of discontinuing the epidural entirely on the outcomes of interest. But such a design would have raised ethical concerns regarding the withholding of effective analgesia. Last, parental opioids are known to induce neurobehavioral depression. The literature regarding the effects of epidural opioids remains unclear.19 However, we did not assess the newborn beyond the routine 1- and 5-min Apgar scores, so, there exists the possibility that this exposure could have resulted in neurobehavioral changes, even subtle ones.

In summary, we found that the use of epidural bupivacaine/fentanyl versus fentanyl-only neither did lengthen the second stage of labor nor did affect the degree of motor blockade, mode of delivery, satisfaction with pain analgesia, and maternal or neonatal outcomes. However, the use of epidural fentanyl-only resulted in a fivefold increase in fetal opioid exposure. Although not assessed, this exposure could result in neonatal neurobehavioral depression, both short and long term, and should be an outcome of interest in future studies. Therefore, anesthetic management should be tailored to the individual needs of the obstetrical patient, balancing the risks and benefits to the mother and her newborn.

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Competing Interests

The authors declare no competing interests.

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