Bupivacaine Augments Intrathecal Fentanyl for Labor Analgesia

Craig M. Palmer, M. D.,* Gretchen Van Maren, M. D.,* Wallace M. Nogami, M. D.,† Diane Alves, R. N.‡

Background: Intrathecal fentanyl has been shown to be an effective analgesic for labor; this study investigated the analgesic effect of low-dose bupivacaine added to intrathecal fentanyl for labor analgesia.

Methods: Ninety parturients in active labor who requested regional analgesia were randomized to receive an intrathecal injection of either fentanyl, 25 μg; bupivacaine, 1.25 mg, with fentanyl, 25 μg; or bupivacaine, 2.5 mg, with fentanyl, 25 μg, as part of a combined spinal-epidural technique. Visual analog pain scores were recorded before and at intervals after injection until the patient requested further analgesia. Maternal blood pressure and fetal heart rate were recorded before injection and at intervals after injection. Lower-extremity muscle strength was tested before and 30 min after injection; anesthetic level to cold sensation and the presence and severity of pruritus were recorded.

Results: Duration of analgesia was longer in the group receiving bupivacaine, 2.5 mg, and fentanyl, 25 μg, than the group receiving plain fentanyl (108 vs. 92 min; P < 0.05). Onset of analgesia was faster in both groups receiving bupivacaine compared with plain fentanyl (P < 0.05). No differences in muscle strength after injection were found in any group, although anesthetic levels to cold were documented in all patients in the bupivacaine groups, and 21 of 30 in the plain fentanyl group. Baseline fetal heart rates did not change after injection in any group, and maternal blood pressure was unchanged.

Conclusions: The addition of 2.5 mg isobaric bupivacaine to 25 μg fentanyl for intrathecal labor analgesia modestly increases duration and speeds onset of analgesia compared with plain intrathecal fentanyl. (Key words: Opioids; pain; parturient; spinal; subarachnoid.)

INTRANAL TH ECAL fentanyl has been shown to be an effective labor analgesic for labor and is often used as part of a combined spinal-epidural technique for this purpose. Although it is effective, shortcomings of the technique include a limited duration of action and occasional side effects, especially pruritus. At cesarean delivery, the use of fentanyl with both bupivacaine and lidocaine has been shown to increase the duration of effective analgesia. For labor analgesia, the addition of bupivacaine to sufentanil has also been reported to increase duration of analgesia.

The purpose of this study was to determine the effect on duration and quality of analgesia of the addition of low-dose bupivacaine to intrathecal fentanyl for labor analgesia.

Methods

Ninety nulliparous full-term parturients classified as American Society of Anesthesiologists physical status 1 and II in active labor gave written, informed consent and participated in this study, which had been approved by our institutional review board. On request for labor analgesia, parturients were randomized (using a table of random numbers) to one of three groups to receive a single intrathecal injection of either fentanyl, 25 μg (Elkins-Sinn, Cherry Hill, NJ; fentanyl-only group); fentanyl, 25 μg, and bupivacaine, 1.25 mg (Abbott Laboratories, North Chicago, IL; fentanyl-bupivacaine 1.25 group); or fentanyl, 25 μg, and bupivacaine, 2.5 mg (fentanyl-bupivacaine 2.5 group) as part of a combined spinal-epidural technique. Parturients with significant coexisting disease (including pregnancy-induced hypertension and gestational diabetes) were excluded from participation, as was any parturient who had received any other form of labor analgesia (intravenous medications) within the preceding hour. Parturients were blinded to their group assignment, as was the investigator making all observations.
INTRATHecal Bupivacaine/Fentanyl For Labor Analgesia

Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Dilation at Placement</th>
<th>Station at Placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl only</td>
<td>24 (5)</td>
<td>163 (6)</td>
<td>84 (17)</td>
<td>4 (1)</td>
<td>-1 (-3 to 2)</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 1.25 mg</td>
<td>25 (6)</td>
<td>163 (7)</td>
<td>81 (15)</td>
<td>3 (1)</td>
<td>-1 (-3 to 0)</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 2.5 mg</td>
<td>22* (5)</td>
<td>164 (7)</td>
<td>81 (13)</td>
<td>3 (1)</td>
<td>-1 (-3 to 0)</td>
</tr>
</tbody>
</table>

Values are mean (SD), except station, which is median (range).

* P < 0.05 versus fentanyl only and bupivacaine 1.25 mg.

After hydration with 500–1000 ml intravenous lactated Ringer’s solution, patients were positioned sitting for placement of a combined spinal–epidural block. An 18-gauge Tuohy needle (B. Braun Medical, Bethlehem, PA) was introduced into the epidural space at the L2-L3, L3-L4, or L4-L5 interspace using the loss-of-resistance technique. A 24-gauge, 120-mm Sprotte needle was placed through the Tuohy needle into the subarachnoid space. After return of clear cerebrospinal fluid, patients received a single intrathecal injection of one of the three solutions noted previously. Bupivacaine 0.25% was used to prepare the injections; all injections were diluted if necessary to a final volume of 1.5 ml with preservative-free normal saline. After the intrathecal injection, the Sprotte needle was withdrawn, and an epidural catheter was threaded 3–5 cm into the epidural space. The Tuohy needle was withdrawn, and the catheter was secured before the patient was repositioned supine with left-uterine displacement. No medications were administered via the epidural catheter until the patient requested further analgesia.

An investigator blinded to the intrathecal injection recorded all observations. Scores on a visual analog pain scale were recorded immediately before injection and at 2.5, 5, 7.5, and 10 min after injection, then every 30 min until the patient requested further analgesia. The scale consisted of an unmarked 10-cm line labeled on the left end with the words “no pain” and on the right end with “worst pain imaginable”: parturients indicated their degree of discomfort by placing a mark on the scale. Scores were measured to the nearest 1 mm (range, 0–100). Maternal blood pressure was measured with an automated blood pressure cuff and recorded immediately before to injection and at 10, 20, and 30 min after injection. Baseline fetal heart rate was recorded before and 30 min after injection. Anesthetic level (sensation of cold to fluoromethane spray) was recorded 15 min after injection; if right and left anesthetic levels were unequal, the level was recorded as the average of the two (i.e., right T6 and left T8 = T7, and so forth). Scores on a visual analog pruritus scale were measured at the same intervals as pain scores (with an unmarked 10-cm line labeled “no itching” on the left end and “worst itching imaginable” on the right end). If a patient’s score was greater than 0, she was asked if she desired treatment.

Assessment of motor block was performed before and at 30 min after injection. Measurements were taken with a force transducer designed to measure global lower extremity muscle strength (see Appendix). This transducer was intended to more accurately and reproducibly quantify lower-extremity muscle strength than other bedside measures.

Duration of analgesia was recorded as the time from injection to the parturient’s first request for further analgesia. If clear, free-flowing cerebrospinal fluid was not obtained after placement of the Sprotte needle, the patient was dropped from the study and her group assignment rerandomized; similarly, if a parturient delivered or reached full cervical dilation (i.e., entered stage 2 of labor) before requesting additional analgesia, she was dropped from the study and the group assignment rerandomized, using a table of random numbers.

Data were analyzed with the Student t test, analysis of variance, two-way analysis of variance, and a posteriori tests as indicated; a P value of 0.05 or less was considered significant.

Results

Ninety patients completed the protocol of this study (n = 30 in each group). The fentanyl-bupivacaine 2.5 group was slightly younger than the other groups, but groups were otherwise demographically similar (table 1).

The duration of analgesia differed significantly between groups (analysis of variance, P = 0.014). Duration of analgesia in the fentanyl-bupivacaine 2.5 group (108 ± 20 min [mean ± SD]) was longer than in the fentanyl-only (92 ± 23 min) and fentanyl-bupivacaine 1.25 groups (94 ± 25 min), which did not differ significantly from each other (fig. 1).

The onset of analgesia (fig. 2) also differed significantly...
Fig. 1. Duration of analgesia (time to first request for additional analgesia). Groups differed significantly (analysis of variance, $P < 0.05$). *Fentanyl-bupivacaine 2.5 group significantly different from fentanyl-only and fentanyl-bupivacaine 1.25 groups, $P < 0.001$. See text for description of groups (mean ± SD).

between groups (two-way analysis of variance, $P < 0.0001$). *A posteriori tests indicated that pain scores were significantly lower at 2.5 min after injection in both bupivacaine groups than the fentanyl-only group, and, further, pain scores were lower in the fentanyl-bupivacaine 2.5 group than in the fentanyl-bupivacaine 1.25 group. At 5 min after injection, both bupivacaine groups were still significantly lower than the fentanyl-only group; by 7.5 min after injection, groups were not significantly different.

Pruritus scores were not significantly different among groups (fentanyl only, 24 ± 4; fentanyl-bupivacaine 1.25, 31 ± 6; fentanyl-bupivacaine 2.5, 19 ± 5; $P = NS$, analysis of variance). Baseline maternal blood pressures did not differ among the groups (table 2). There were no significant changes within groups in maternal systolic blood pressure. Diastolic blood pressure change occurred only in the fentanyl-bupivacaine 1.25 group (analysis of variance, $P < 0.01$); a significant difference was found only between the baseline and 30-min postinjection values ($P < 0.05$).

There was no difference between groups in baseline fetal heart rate; likewise, there was no difference among groups in fetal heart rate at 30 min postinjection (analysis of variance, $P = NS$). Within each group, there were no differences in fetal heart rates between preinjection and postinjection values. Transient fetal heart rate changes were noted in eight parturients during the course of the study, and fetal monitor strips from these parturients were reviewed retrospectively (table 3). In all cases these changes resolved spontaneously, and none required urgent or emergent obstetric intervention.

Lower-extremity muscle strength scores are shown in table 4. Baseline scores were not significantly different among groups, nor were postinjection scores (analysis of variance, $P = NS$). No differences were found in mean score before and after injection in any group.

An anesthetic level to cold spray was found in all parturients in the fentanyl-bupivacaine 1.25 and fentanyl-bupivacaine 2.5 groups (mean levels T6 and T5, respectively); an anesthetic level was also documented in 21 of 30 (mean level T6) parturients in the fentanyl-only group.

Regarding ultimate mode of delivery, overall cesarean delivery rate was 5.6% (5 of 90 patients); the indication was cephalopelvic disproportion in three cases and arrest of labor in two others. There was no difference between groups in mode of delivery (vaginal vs. cesarean).

**Discussion**

Intrathecal fentanyl has become popular for labor analgesia in recent years. At a dose of 25 μg, fentanyl...
INTRATHECAL BUPIVACAINE/FENTANYL FOR LABOR ANALGESIA

Table 2. Maternal Blood Pressures

<table>
<thead>
<tr>
<th>Group</th>
<th>Preinjection</th>
<th>Postinjection 10 min</th>
<th>Postinjection 20 min</th>
<th>Postinjection 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl only</td>
<td>120 ± 9</td>
<td>71 ± 6</td>
<td>67 ± 8</td>
<td>66 ± 9</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 1.25 mg</td>
<td>121 ± 12</td>
<td>118 ± 17</td>
<td>123 ± 12</td>
<td>124 ± 13</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 2.5 mg</td>
<td>119 ± 10</td>
<td>118 ± 17</td>
<td>123 ± 12</td>
<td>124 ± 13</td>
</tr>
</tbody>
</table>

Values are mean ± SD (mmHg).

* P < 0.05 versus preinjection diastolic BP, a posteriori.

provides analgesia of relatively rapid onset with a mean duration of approximately 90 min. Side effects are usually easily managed, and there is no associated motor block.

In an effort to improve analgesia and duration, bupivacaine has been reported as an adjunct to intrathecal fentanyl for labor.\(^5,6\) Previous reports have not compared the combination to plain intrathecal fentanyl, or to lower doses of intrathecal bupivacaine, however. This series was undertaken to clearly define the benefits from, and appropriate dose of, bupivacaine if used with intrathecal fentanyl.

Our findings indicate that adding isobaric bupivacaine, 2.5 mg, to intrathecal fentanyl, 25 µg, significantly prolongs the duration of effective analgesia to a mean of 108 min, compared with a mean of 92 min after plain fentanyl, 25 µg. A second notable finding is the increased speed of onset of the combinations compared with plain

Table 3. Detail of Fetal Heart Rate Change

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient Number</th>
<th>Type of Change</th>
<th>Duration Labor Postinjection (h)</th>
<th>Oxytocin, Rate (mU/min)</th>
<th>Prior Decel's</th>
<th>Apgars (1, 5 min)</th>
<th>Labor, Spontaneous or Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl only</td>
<td>43</td>
<td>One variable deceleration</td>
<td>3.5</td>
<td>Yes (20)</td>
<td>No</td>
<td>8, 8</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>27 min postinjection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isolated deceleration to 90 bpm, 13 min after injection</td>
<td>4</td>
<td>No</td>
<td>Yes: variable</td>
<td>8, 9</td>
<td>S</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 1.25 mg</td>
<td>16</td>
<td>Isolated deceleration to 90’s 10 min after injection</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>8, 9</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>Isolated deceleration 8 min postinjection</td>
<td>3.5</td>
<td>Yes (12)</td>
<td>No</td>
<td>9, 9</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Isolated deceleration to 80’s, 15 min postinjection</td>
<td>7 (C/S-arrest of labor)</td>
<td>Yes (N/A)</td>
<td>Yes: variable</td>
<td>9, 9</td>
<td>I</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 2.5 mg</td>
<td>15</td>
<td>Several “late” decelerations associated with nausea and vomiting 26 min postinjection</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>7, 8</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4 “late” decelerations 18 min postinjection associated with decreased BP (84/42)</td>
<td>3</td>
<td>Yes (8)</td>
<td>Yes: early and variable</td>
<td>8, 9</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Isolated decelerations to 70 and 90 bpm, 15 and 20 min postinjection</td>
<td>6</td>
<td>Yes (4)</td>
<td>Yes: early and variable</td>
<td>9, 9</td>
<td>I</td>
</tr>
</tbody>
</table>

N/A = not available; BP = blood pressure.

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Table 4. Lower Extremity Muscle Strength Scores, Pounds
Pressure Exerted

<table>
<thead>
<tr>
<th></th>
<th>Preinjection</th>
<th>Postinjection</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl only</td>
<td>87 (31)</td>
<td>93 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 1.25 mg</td>
<td>98 (36)</td>
<td>110 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Fentanyl + bupivacaine 2.5 mg</td>
<td>93 (33)</td>
<td>95 (33)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.
Values are mean (SD).
* Student t test, preinjection versus postinjection values.

Although we did find diastolic blood pressure to be statistically lower in the fentanyl-bupivacaine 1.25 group at 30 min after injection, we do not believe this is clinically significant, and it may represent a chance finding.

Although this series demonstrated a statistically significant increase in duration and speed of onset of analgesia, it would also likely increase motor block, eliminating one of the technique’s advantages. Although we did find diastolic blood pressure to be statistically lower in the fentanyl-bupivacaine 1.25 group at 30 min after injection, we do not believe this is clinically significant, and it may represent a chance finding.

Although this series demonstrated a statistically significant increase in duration and speed of onset of analgesia, it can be argued that the clinical significance of the findings remains to be proven. Although the increase in duration demonstrated is relatively short, the protocol was biased toward parturients with longer, more painful labors because of the exclusion of parturients who entered the second stage of labor. This would lead to a conservative estimate of duration and should be considered in comparisons with other series. The faster onset, though dramatic, actually represents a difference of 5 min or less over plain fentanyl. The ultimate clinical significance of our findings must be considered in each practice setting, for each parturient.

Although intrathecal opioids should have no effect on motor pathways or muscle strength, local anesthetics can cause motor block. Previous reports have indicated that this combination (fentanyl, 25 μg, and bupivacaine, 2.5 mg) has little effect on motor pathways; Collis et al. reported 100% of parturients receiving this combination able to perform a straight leg raise against resistance. Shennan et al., in a series of 62 patients, noted that “all were judged...capable of ambulating.” Traditional tests to assess motor strength (Bromage score, straight leg raising) may not be well suited to assessing minimal degrees of motor block; this has led to the description of a modified Bromage scale, which is more sensitive. Scoring on this modified Bromage scale requires a patient to get out of bed, however, a chore that is not always welcomed during painful labor. For this reason, we developed the system described in the Appendix to allow measurement of baseline (and serial) lower-extremity muscle strength scores. In this series, this provided reliably reproducible measurements of strength, and we were unable to detect any significant change in muscle strength in any of the three groups studied.

Sufentanil has been reported to be associated with sensory changes. Cohen et al. reported decreased sensation to cold and pinprick in 17 of 18 patients who received sufentanil, 10 μg, for intrathecal labor analgesia. Although we expected sensory changes in the groups receiving bupivacaine, we were surprised to find decreased cold sensation in most of the parturients (21 of 30) who received plain intrathecal fentanyl. Such sensory changes associated with intrathecal fentanyl have not been reported previously and may indicate that these sensory changes are characteristic of all opioids administered intrathecally.

Ambulation during labor has become increasingly popular in recent years, and so-called walking epidural techniques often incorporate an intrathecal injection of opioid, sometimes combined with local anesthetic. Although no motor block that would preclude ambulation was detected consistently in any of the three groups in this study, the decreased sensation to cold that was found in all three groups raises the possibility that proprioception may be significantly affected. If this technique is used in a parturient with the expectation of ambulation, she should be carefully evaluated and closely monitored for not only motor strength but also sufficient lower-extremity sensation.

The possibility that intrathecal fentanyl might be associated with fetal heart-rate abnormalities was initially raised by Clarke et al. Subsequently, Collis et al. noted no difference between intrathecal fentanyl and standard epidural groups in the rate of fetal bradycardia after injection (13% vs. 9%). Richardson reported one fetal heart-rate trace (of 20) worsened after intrathecal fentanyl injection (5%). Palmer et al. compared intrathecal fentanyl and standard epidural techniques for labor and found no difference between the two groups in the incidence of fetal heart-rate abnormality, and no effect on need for urgent delivery or ultimate delivery route. The protocol for this series was established prior to initial reports of fetal heart-rate changes, and therefore looked only at the less sensitive and nonstandard measure, mean fetal heart rate. As this series was not intended to evaluate the effects of intrathecal analgesia on fetal heart rates, our findings should be viewed with caution; the reports noted here indicate that the eight transient fetal heart-rate changes observed in this series.
are likely within the normal range of incidence of such events after institution of regional anesthesia for labor.

In summary, two combinations of fentanyl and bupivacaine were compared with plain fentanyl for intrathecal labor analgesia. The combination of fentanyl, 25 μg, and bupivacaine, 2.5 mg, prolonged duration and hastened onset compared with fentanyl, 25 μg, alone. Motor strength was not found to be significantly affected, although sensory changes that may alter proprioception were found in all groups.

Appendix

The most common means of assessment of muscle strength after regional anesthesia is the Bromage scale,13 which tests the strength of lower extremity muscle groups against gravity. As techniques have evolved and use of low concentrations of local anesthetics and opioids has become common, the lack of sensitivity of this scale has led to development of other scales to detect more subtle degrees of motor impairment. One such scale is the modified Bromage scale, proposed by Breen et al.14 A shortcoming is that it requires the patient (parturient) to get out of bed and perform a deep knee bend at bedside. This can be an onerous chore to laboring parturients (and their nurses) and can interfere with continuous tocodynamometry and fetal heart-rate monitoring.

Apparatus for measurement of muscle strength has been described by Ilsley et al.,15 but it is relatively expensive and requires an electrical source. We devised the system depicted in figure 3 as an inexpensive, easily constructed, "low-tech" approximation of Ilsley et al.'s force meter. It allows easy serial assessments without the need to get out of bed and without disturbing fetal or uterine monitoring.

The apparatus consists of a strain gauge, in this case a bathroom scale (Detecto, Cardinal Scale Manufacturing, Webb City, MO) affixed to a plywood platform. The platform is secured in a fixed vertical position to the foot of the patient's bed. The patient is recumbent at an approximately 45° angle; she is instructed to hold the side rails of the bed with arms straight and elbows locked. Her feet are placed flat on the scale, with both hips and knees partially flexed. To test lower extremity muscle strength, she is instructed to press down on the scale with her legs as hard as possible. The highest reading on the scale is noted. The force applied to the scale represents the combined force of hip and knee extensor muscle groups, roughly the same muscle groups tested in performing a deep knee bend (fig. 3).

Fig. 3. Use of the lower-extremity muscle-strength device. With the patient's feet placed flat on the vertical strain gauge (bathroom scale) and with arms fully extended and hands grasping the bed's handholds, the patient is instructed to press down on the scale as hard as possible. The effort is scored as the highest number registered. The primary muscle groups tested are the hip extensors (gluteus maximus-I3, L1 and adductor magnus-L3, L4) and the knee extensors (vastus muscle group-L3, L4, and the tensor fascia lata-L5).

References