Intrathecal Morphine 0.2 mg versus Epidural Bupivacaine
0.125% or Their Combination: Effects on Parturients

Ezzat Abouleish, M.D.,* Narinder Rawal, M.D., Ph.D.,† James Shaw, M.D.,‡
Tim Lorenz, M.D.,‡ M. Nabil Rashad, M.D., Ph.D.§

To compare the efficacy and side effects of 0.2 mg intrathecal (IT) morphine with 0.125% epidural bupivacaine, 62 women in labor were studied. They were randomly divided into three groups: group 1 (n = 20) received IT morphine; group 2 (n = 22) received epidural bupivacaine; and group 3 (n = 20) received a combination of both using a combined spinal–epidural (CSE) technique. According to a visual analogue scale for assessing analgesia, neither IT 0.2 mg morphine nor 10 ml 0.125% epidural bupivacaine was effective in producing adequate pain relief in labor, whereas the combination produced excellent analgesia. The use of IT morphine significantly reduced the dosage requirement of epidural bupivacaine. The incidence of nausea, vomiting, and pruritus was significantly higher when IT morphine had been administered, whereas that of urinary retention did not differ. No serious respiratory depression occurred in any of the patients. When the course of labor was studied, the prior use of IT morphine significantly prolonged the duration of the first stage of labor and the total duration of labor. We conclude that the administration of 0.2 mg IT morphine in combination with epidural administration of 0.125% bupivacaine provides better analgesia than the administration of either drug alone. (Key words: Analgesics, opioid: morphine. Anesthesia: obstetric. Anesthetic techniques: epidural; spinal. Anesthetics, local: bupivacaine.)

INTRATHecal (IT) MORPHINE in a dose of 0.5–2 mg has been used for pain control during labor.1–3 However, a dose of 0.3 mg or more carries the risk of respiratory depression.4,5 Therefore, a dose of less than 0.3 mg IT morphine is preferable. Epidural bupivacaine 0.125% is also considered effective for pain control during labor.6 It has been demonstrated that the combination of local anesthetics and opioids administered epidurally allows the use of a lower concentration of the local anesthetic.7 However, it is unclear if such an action also occurs when intrathecal opioids and an epidural local anesthetic are administered simultaneously. The purpose of this study is twofold:

1. to compare 0.2 mg IT morphine with 0.125% bupivacaine in regard to analgesia and side effects during labor; and
2. to determine whether the combination has a better analgesic action than either one alone.

Materials and Methods

The study consisted of 62 patients randomly divided into three groups. Group 1 (n = 20) received 0.2 mg IT morphine; group 2 (n = 22) received 10 ml epidural bupivacaine 0.125%; and group 3 (n = 20) received a combination of IT morphine and epidural bupivacaine. All patients were ASA Physical Status 1, had full-term pregnancy, and were carrying a normal fetus with cephalic presentation. The initial plan was to conduct a double-blind study in which every patient would have both subarachnoid and epidural puncture and receive either the study drug or normal saline. However, it was considered unjustifiable to expose the patients receiving only epidural bupivacaine (group 2) to the added risks of lumbar puncture. Therefore, in the final form of the study and as presented here, the investigators were not blinded to the groups; however, the patients, the obstetricians, the nursing staff, and the neonatologists were unaware of the group assignment. With this foreseen limitation, the study was approved by the university and hospital human research committees, and all patients gave written consent.

When analgesia was requested by the patient during the course of labor, either IT morphine, epidural bupivacaine, or the combination was administered depending on the group assignment. In patients receiving IT morphine alone or in combination with epidural bupivacaine, a combined spinal and epidural technique (CSE), described in detail elsewhere, was applied.8,9 Briefly, the epidural space was identified using an 18-G, 8.125-cm (3.25-inch) Tuohy needle. A 26-G, 11.875-cm (4.75-inch) spinal needle was introduced through the Tuohy needle and the dura was penetrated. Morphine was injected intrathecally, after which the spinal needle was removed. An epidural catheter (20-G) was subsequently introduced through the Tuohy needle, and the Tuohy needle was then withdrawn. The epidural catheter was firmly secured in place using adhesive tape.

After administration of the drug(s) as described above, analgesia was evaluated every 10 min for 1 h and then

* Professor of Anesthesiology and Obstetrics and Gynecology, Department of Anesthesiology, the University of Texas Medical School at Houston.
† Orebro Medical Center Hospital, Orebro, Sweden.
‡ Resident in Anesthesiology, the University of Texas Medical School at Houston.
§ Assistant Professor, Department of Anesthesiology, Baylor College of Medicine at Houston, Houston, Texas.

Received from the Department of Anesthesiology, University of Texas at Houston, Houston, Texas. Accepted for publication December 18, 1990. Presented in part at the 64th Congress of International Anesthesia Research Society, Honolulu, Hawaii, March 1990.

Address reprint requests to Dr. Abouleish: 6451 Fannin, MSB 5.020, Department of Anesthesiology, Houston, Texas 77030.
TABLE 1. Age, Parity, Gestational Age, and Obstetric Condition at the Start of Drug Administration

<table>
<thead>
<tr>
<th></th>
<th>IT Morphine (n = 20)</th>
<th>Epidual Bupivacaine (n = 22)</th>
<th>Both (CSE) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28.4 ± 1.4</td>
<td>26.9 ± 1.4</td>
<td>24.4 ± 1.3</td>
</tr>
<tr>
<td>Nullipara (n)</td>
<td>10</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Multipara (n)</td>
<td>10</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.4 ± 0.4</td>
<td>38.5 ± 2.6</td>
<td>39.5 ± 0.4</td>
</tr>
<tr>
<td>Cervical dilation (cm)</td>
<td>4.5 ± 1.5</td>
<td>4.0 ± 1.4</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>Cervical effacement (%)</td>
<td>85 ± 18</td>
<td>85 ± 23</td>
<td>72 ± 29</td>
</tr>
<tr>
<td>Fetal head station</td>
<td>−1.3 ± 0.5</td>
<td>−1.8 ± 1.1</td>
<td>−1.4 ± 0.5</td>
</tr>
</tbody>
</table>

Mean ± SEM.
There were no significant statistical differences between groups.

The data were expressed as mean ± standard error of the mean (SEM). For comparison of qualitative data, e.g., analysis of side effects, chi-squared analysis was applied, and for comparison of quantitative data, e.g., duration of labor, analysis of variance was used. The medians of the pain scores were compared using the Kruskal-Wallis test. A P value < 0.05 was considered statistically significant.

**Results**

Age, parity, and gestational age were similar in the three groups (table 1). Neither IT morphine alone nor 10 ml 0.125% epidural bupivacaine provided adequate analgesia, since the majority of these patients at 40 min were in pain and required additional administration of local anesthetic (fig. 1; table 2). On the other hand, patients in group 3 (given a combination of IT morphine and epidural bupivacaine) had excellent analgesia within 20 min. At 60 min, all patients were equally comfortable because of the addition of an adequate amount of local anesthetics. The prior administration of 0.2 mg IT morphine reduced significantly the dose requirement of epidural bupivacaine per hour (table 2).

At the start of administration of the analgesic drugs, there was no difference among the groups regarding the cervical dilatation, cervical effacement, or fetal head sta-

![Fig. 1. Comparison of the medians of pain scores during labor. Doses: 0.2 mg intrathecal morphine; 10 ml epidural bupivacaine 0.5%; or combination of both (CSE). *Significant statistical difference from the other two groups. P < 0.05.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931343/ on 06/19/2017)
TABLE 2. Effect of Intrathecal Morphine on Epidural Local Anesthetic Requirement

<table>
<thead>
<tr>
<th></th>
<th>IT Morphine (n = 20)</th>
<th>Epidural Bupivacaine (n = 22)</th>
<th>Both (CSE) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine dose</td>
<td>8.4 ± 2.5</td>
<td>15.8 ± 2.0*</td>
<td>6.9 ± 0.7</td>
</tr>
<tr>
<td>requirement (mg·h⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients requiring second dose at 40 min</td>
<td>16 (80%)</td>
<td>13 (65%)</td>
<td>4 (20%)*</td>
</tr>
</tbody>
</table>

Mean ± SEM. *Significant statistical difference from the other two groups, P < 0.05.

Discussion

In the current study, IT morphine (0.2 mg) or low-concentration bupivacaine (0.125%) were not effective in relieving labor pains. In contrast, their combination was quite effective and was clearly superior to either one alone. Thus, our results confirm that spinal opioids render subanalgiesic concentrations of local anesthetic efficacious.7,11,12 The potentiation of subanalgiesic local anesthetic has the advantages of preserving motor power and sustaining the stability of the cardiovascular system. However, it should be noted that in the current study the opioid was morphine and not fentanyl7 or sufentanil,11,12 and that the route of its administration was intrathecal and not epidural. The advantages of the CSE technique using morphine are the need for only a single subarachnoid injection of a minute dose and the prolonged duration of analgesia, lasting the whole course of labor.

However, the combined IT morphine and epidural bupivacaine has disadvantages that should be taken into consideration. The side effects, namely pruritus, nausea, and vomiting, were increased by the addition of IT morphine. However, they were mild: most of them were revealed only by questioning the patients, and treatment was not required in the majority of cases. The incidence of urinary retention in this study was not increased by the addition of 0.2 mg IT morphine. The mechanical effect of the advancing fetal head in the intrapartum period and the traumatic effect of vaginal delivery on the urethra and base of bladder in the postpartum period play a major role in urinary retention and need for catheterization in obstetrics.13

In a previous study using pulse oximetry for 24 h to monitor ventilation after cesarean section, SPO₂ remained above 90% in only 9% of patients who were breathing room air and receiving parenteral narcotics.14 Also, during sleep, oxygen saturation significantly decreases.15,16 For these reasons, we arbitrarily used 85% SPO₂ or a respiratory rate of ≤10 breaths per min or both to indicate respiratory depression requiring treatment. It has been suggested that pain relief produced by epidural local anesthetic after IT morphine may cause respiratory depres-

TABLE 3. Incidence and Indications of Cesarean Section

<table>
<thead>
<tr>
<th></th>
<th>IT Morphine (n = 20)</th>
<th>Epidural Bupivacaine (n = 22)</th>
<th>Both (CSE) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>16 (80%)</td>
<td>18 (81%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>4 (20%)</td>
<td>4 (19%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystocia</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Abruption</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no significant statistical differences between groups.
sion. In this study, the SpO₂ and the respiratory rate were well above the critical set levels, and no patient suffered from respiratory depression. The small dose of IT morphine, the young age of our patients, their healthy condition, and the respiratory stimulating effect of progesterone are contributing factors for its safety. However, because of the rarity of respiratory depression with IT morphine (incidence of 3 per 1,000), a considerably larger number of patients have to be studied before the safety of this technique can be established unequivocally.

With CSE, there is a potential risk that the epidural catheter will penetrate through the dural hole made by the spinal needle. In experimental studies on isolated human dura, it was impossible to force an 18-G epidural catheter through dural holes made by spinal needles 22-G or finer. This has been reflected in the results of investigators with extensive experience with CSE block. Only one catheter penetration of the dura occurred during a 6-yr period in which about 4,000 CSE blocks were performed. Similar to all cases of epidural block, there is always a risk that the epidural catheter will migrate into the subdural or subarachnoid space. Therefore, precautions should be taken to confirm the proper position of the catheter with intermittent injections, and the level of the block should be assessed repeatedly with continuous epidural infusions.

The incidence of post lumbar puncture cephalgia in obstetrics can reach 25% even with a 26-G spinal needle. The incidence in our study was 2.5% after intrathecal morphine and epidural bupivacaine. Although there are no data from controlled studies, several investigators have commented on the very low incidence of post lumbar puncture cephalgia after CSE block. There are several possible mechanisms. First, the Tuohy needle in the epidural space serves as an introducer, such that the spinal block is easier to perform and multiple attempts to identify the subarachnoid space can be avoided. Second, the technique allows the use of fine-diameter spinal needles. Third, the increased epidural pressure resulting from injection of local anesthetics reduces the CSF leakage. Fourth, it is possible that the spinal opioid reduces the incidence of headache.

Examination of the course of labor revealed a surprising result. In patients in groups 1 and 3, who received morphine, duration of the first stage and the whole course of labor was prolonged, but the duration of the second stage of labor was not. Therefore, it appears that IT morphine depressed uterine contractions but did not interfere with the ability of the mother to bear down. The mechanism underlying such an effect may one or more of the following.

First, an action at the hypothalamic–pituitary level is suggested by a central action of morphine. Bicknell et al. showed that injection of 18 µg morphine sulfate into the lateral ventricle of primiparous Sprague-Dawley rats caused a severe delay in parturition associated with a significant reduction of blood plasma oxytocin levels. This effect was prevented by subcutaneous administration of naloxone and overcome by intravenous infusion of 4–10 ng/min oxytocin. Second, a spinal cord site of action similar to the effect of morphine on micturition is possible. Rawal et al. found that epidural injection of morphine in

<table>
<thead>
<tr>
<th>Duration of first stage (h)</th>
<th>Nullipara (n = 9)</th>
<th>Multipara (n = 7)</th>
<th>Nullipara (n = 9)</th>
<th>Multipara (n = 7)</th>
<th>Nullipara (n = 9)</th>
<th>Multipara (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of second stage (h)</td>
<td>10.5 ± 1.3</td>
<td>11.3 ± 3.1</td>
<td>6.5 ± 0.8*</td>
<td>5.2 ± 0.6*</td>
<td>11.1 ± 0.2</td>
<td>9.4 ± 0.8</td>
</tr>
<tr>
<td>Total duration of labor (h)</td>
<td>13.0 ± 0.4</td>
<td>0.8 ± 0.2</td>
<td>0.5 ± 0.1</td>
<td>0.3 ± 0.03</td>
<td>1.1 ± 0.3</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>The time interval between first</td>
<td>11.8 ± 1.4</td>
<td>11.9 ± 3.3</td>
<td>7.1 ± 0.9*</td>
<td>5.5 ± 0.6*</td>
<td>12.2 ± 1.0</td>
<td>9.9 ± 0.7</td>
</tr>
<tr>
<td>administration of analgesia</td>
<td>6.1 ± 1.3</td>
<td>3.4 ± 0.7</td>
<td>2.6 ± 0.7*</td>
<td>2.1 ± 1.2†</td>
<td>5.5 ± 1.1</td>
<td>6.1 ± 0.7</td>
</tr>
</tbody>
</table>

Mean ± SEM.
* Significantly shorter than the IT morphine group, P < 0.05.
† Significantly shorter than the CSE group, P < 0.05.

<table>
<thead>
<tr>
<th>IT Morphine (n = 20)</th>
<th>Epidural Bupivacaine (n = 22)</th>
<th>Both (CSE) (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO₂ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;95</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>&lt;94, &gt;90</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>&lt;90</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>&gt;12</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>&gt;10, &lt;12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no significant differences between groups.
* SpO₂ 88%.

† Svante Lindén: Liddevalla, Sweden, personal communication.
male volunteers caused depression of detrusor muscle function for many hours by acting locally on the spinal cord.\textsuperscript{28} Third, morphine can act on opioid receptors in the uterus itself.\textsuperscript{24,25} Faletti \emph{et al.},\textsuperscript{24} in \textit{in vitro} studies of the effect of morphine on uterine strips of oophorectomized rats, found decreased uterine contractility and interference with the stimulating effect of exogenous prostaglandin E\textsubscript{2} but not with prostaglandin F\textsubscript{2}. The basal synthesis of prostaglandins E and F \emph{in utero} from oophorectomized rats was significantly depressed by morphine but was not altered by incubation of tissues with morphine in the presence of naloxone.\textsuperscript{24} Also, \textit{in vitro} studies showed that morphine decreased the frequency of contractions of rats’ estrus uterus, whereas meperidine and pentazocine enhanced it.\textsuperscript{25}

Since only a minute dose of intrathecal morphine was used, a direct effect on uterine opioid receptors is unlikely, and action on the spinal cord or hypothalamus or both is the most probable cause. Careful examination of the results of previous studies on intrathecal morphine showed some evidence of a depressing effect of IT morphine on uterine contractions. Baraka \emph{et al.} stated that unlike the parturients in the 1-mg morphine group, in 8 of the 13 parturients given 2 mg morphine (61.5%), labor was augmented by oxytocin infusion, and the difference was statistically significant ($P \leq 0.01$).\textsuperscript{2} Abboud \emph{et al.} found that

|TABLE 6. Side Effects|

<table>
<thead>
<tr>
<th></th>
<th>IT Morphine</th>
<th>Epidual Bupivacaine</th>
<th>Both (CSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 20$)</td>
<td>($n = 22$)</td>
<td>($n = 20$)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 (20%)</td>
<td>0 (0%)*</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Treated</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 (25%)</td>
<td>0 (0%)*</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Treated</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6 (30%)</td>
<td>1 (4%)*</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Treated</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Post-lumbar puncture cephalgia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Postpartum urinary retention (after exclusion of Cesarean section)</td>
<td>5/16 (31%)</td>
<td>4/18 (22%)</td>
<td>5/15 (33%)</td>
</tr>
</tbody>
</table>

* Significant statistical difference from the other two groups, $P < 0.05$.

|TABLE 7. Fetal Outcome|

<table>
<thead>
<tr>
<th></th>
<th>IT Morphine</th>
<th>Epidual Bupivacaine</th>
<th>Both (CSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>($n = 20$)</td>
<td>($n = 22$)</td>
<td>($n = 20$)</td>
</tr>
<tr>
<td>Apgar scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>1 min 5 min</td>
<td>1 min 5 min</td>
<td>1 min 5 min</td>
</tr>
<tr>
<td>6–7</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>8–10</td>
<td>1 1</td>
<td>21 22</td>
<td>20 20</td>
</tr>
<tr>
<td>Blood gas and acid–base status of umbilical arterial blood (mean ± SEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.25 ± 0.02</td>
<td>7.22 ± 0.03</td>
<td>7.26 ± 0.02</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>17.2 ± 2</td>
<td>17.6 ± 2</td>
<td>18.4 ± 3</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>59.6 ± 3</td>
<td>57.6 ± 3</td>
<td>51.0 ± 4</td>
</tr>
<tr>
<td>Base excess</td>
<td>−3.0 ± 0.7</td>
<td>−4.4 ± 1.0</td>
<td>−2.8 ± 0.8</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25.0 ± 0.6</td>
<td>23.6 ± 0.7</td>
<td>24.0 ± 0.5</td>
</tr>
<tr>
<td>Blood gas and acid–base status of umbilical venous blood (mean ± SEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.31 ± 0.02</td>
<td>7.29 ± 0.02</td>
<td>7.33 ± 0.01</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>28.5 ± 2</td>
<td>29.0 ± 2</td>
<td>29.5 ± 3.5</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>47.6 ± 3</td>
<td>45.6 ± 3</td>
<td>43.3 ± 1.1</td>
</tr>
<tr>
<td>Base excess</td>
<td>−3.7 ± 0.6</td>
<td>−3.8 ± 0.9</td>
<td>−2.0 ± 0.7</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>23.3 ± 0.5</td>
<td>21.8 ± 0.5</td>
<td>23.3 ± 0.7</td>
</tr>
</tbody>
</table>

There were no significant differences between groups.
the need for oxytocin during labor was 40% in parturients receiving 0.5 mg IT morphine compared to 70% in those receiving 1 mg IT morphine; although the difference was statistically insignificant because of the small number of patients, the trend was evident. Unfortunately, in these studies, there was no control group in which IT morphine was avoided.

Since our finding of the possible depressing effect of IT morphine on the course of labor was not planned and was not the primary goal, a controlled blinded prospective study of such an important and specific combination should be performed. Such a study should include a large number of parturients in order to demonstrate clearly and definitely the effect on nulliparous as well as on multiparous patients, each as a separate group.

In conclusion, this study has shown that neither 0.2 mg IT morphine nor 10 ml 0.125% epidural bupivacaine alone was effective in controlling pain during labor, whereas the combination of the two provided effective analgesia and reduced the local anesthetic requirement. However, the side effects and the possible prolongation of labor should be taken into consideration.

The authors would like to acknowledge Jean Haymon and Deborah Vinson for their invaluable secretarial help.

References