Addition of Epinephrine to Intrathecal Bupivacaine and Sufentanil for Ambulatory Labor Analgesia


Background: The intrathecal combination of sufentanil and bupivacaine provides rapid, effective analgesia for labor with a limited duration. Many anesthesiologists have concerns that the use of intrathecal local anesthetics precludes maternal ambulation. This prospective, randomized, double-blind study was designed to determine whether the addition of epinephrine to the combination of sufentanil and bupivacaine would prolong intrathecal analgesia for labor. Patients' ability to ambulate was also assessed.

Methods: Thirty-nine patients received either an intrathecal control dose of 10 μg sufentanil plus 2.5 mg bupivacaine plus 0.2 ml normal saline (control group); or 10 μg sufentanil plus 2.5 mg bupivacaine plus 0.2 ml (0.2 mg) of epinephrine (EPI group).

Results: Seven patients (3 control, 4 EPI) delivered vaginally and two (1 control, 1 EPI) required cesarean delivery before requesting epidural analgesia. The duration (mean ± SD) of intrathecal labor analgesia was prolonged significantly by the addition of epinephrine: control (n = 15): 145 ± 23 min; EPI (n = 19): 188 ± 25 min (P < 0.0001). Maternal ambulation was demonstrated in 100% (19 of 19) of the control group and in 80% (16 of 20) of the EPI group (P = NS).

Conclusions: The addition of 0.2 mg epinephrine to the intrathecal combination of sufentanil and bupivacaine significantly prolonged labor analgesia without causing adverse effects to the mother or fetus. The intrathecal combination of sufentanil and bupivacaine, with or without epinephrine, provided rapid, profound labor analgesia and allowed most patients to ambulate. (Key words: Analgesics, opioids: sufentanil.

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Anesthesia, obstetric, Anesthetic techniques: combined spinal-epidural; epidural; spinal.)

INTRATECAL opioids, a popular and effective means of providing labor analgesia, are commonly administered using the combined spinal-epidural (CSE) technique. This technique affords rapid, profound analgesia using intrathecal medications and allows the anesthesiologist to provide additional analgesia or anesthesia via the epidural catheter. Intrathecal sufentanil provides nearly instantaneous pain relief, but its duration of analgesia is relatively short.1,2 A recent study evaluated the addition of 2.5 mg bupivacaine to 10 μg sufentanil using the CSE technique for intrathecal analgesia for labor.3 The authors showed that this combination significantly improved and prolonged labor analgesia in nulliparous patients without causing adverse effects to the mother or fetus. The combination of 1 mg bupivacaine, 5 μg sufentanil, and 25 μg epinephrine was recently reported4 to provide adequate (Visual Analog Scale [VAS] < 25) intrathecal analgesia for a similar duration as documented for the higher doses of the intrathecal combination of sufentanil (10 μg) and bupivacaine (2.5 mg).5 Although motor weakness was not detected in either investigation,5,4 neither study design evaluated patients' ability to ambulate. The addition of 0.2 mg intrathecal epinephrine, which traditionally has been used to prolong the duration of action of local anesthetics,5,8 has also been used as the sole agent to provide labor analgesia.9 Epinephrine (0.2 mg) did not, however, significantly prolong labor analgesia when combined with 10 μg intrathecal sufentanil.10,11 The addition of 0.2 mg epinephrine to 2.5 mg intrathecal bupivacaine and 10 μg sufentanil has not been evaluated previously. Thus this prospective, randomized, double-blind study was designed to determine whether the addition of 0.2 mg epinephrine to the intrathecal combination of 2.5 mg bupivacaine and 10 μg sufentanil would prolong labor analgesia.
Methods

After institutional review board approval and written, informed consent were obtained, 39 nulliparous full-term parturients, classified as American Society of Anesthesiologists physical status 1 or 2, who requested epidural analgesia were recruited. Only patients in established labor requesting epidural analgesia with cervical dilatation less than 5 cm and normal fetal heart rate (FHR) tracings were considered. Of note, determination of cervical dilatation was required within 30 min of recruitment. Each patient was randomized, using a computer-generated randomization table, to receive one of two intrathecal study solutions. The study solutions consisted of either 1 ml 0.25% (2.5 mg) bupivacaine (Sensorcaine; Astra Pharma, Mississauga, Ontario) plus 10 μg sufentanil (Janssen Pharmaceutica, Markham, Ontario) plus 0.2 ml 0.9% saline (control group); or 2.5 mg bupivacaine plus 10 μg sufentanil plus 0.2 ml (0.2 mg) epinephrine (Abbott Laboratories, Toronto, Ontario) (EPI group). Each intrathecal study solution consisted of a total volume of 2.2 ml. The solutions were prepared using preservative-free 0.9% saline by an anesthesiologist not involved in the study.

Each patient received at least 1,000 ml of a balanced salt solution before the CSE was begun. The procedure was performed at either the L2–3 or L3–4 interspace, with all patients in the sitting position. The CSE involved locating the epidural space with a 17-G epidural needle using a loss-of-resistance-to-air technique. A 25-G Whitacre (4–11/16 inch) spinal needle (Becton-Dickinson, Rutherford, NJ) was passed through the epidural needle. After clear, free-flowing cerebrospinal fluid was identified, the study solution was injected through the spinal needle. Each patient received one of the two study solutions in a double-blind manner. If cerebrospinal fluid was not identified, then the study solution was not injected and the patient was excluded from the study. The 25-G spinal needle was subsequently removed and a 20-G epidural catheter was inserted 3–4 cm into the epidural space. Aspiration was attempted from the epidural catheter in an effort to detect either inadvertent intravascular or intrathecal placement. However, the customary epidural local anesthetic test dose was not administered due to its potential to confound the evaluation of the study solutions. Upon securing the epidural catheter, left uterine displacement was implemented and the head of the bed was elevated to approximately 20–30 degrees.

Hypotension, defined as a systolic blood pressure less than 90 mmHg or a 20% decrease from baseline, was to be treated immediately with a fluid bolus and intravenous ephedrine as required.

The duration of analgesia was defined as the time from the intrathecal injection of the study solution until the patient requested additional analgesia via the epidural catheter.

After administration of the study solution, each patient was evaluated by an investigator blinded to the study solution. Patients were assessed every 5 min for the first 15 min and then every 15 min until additional medication was requested via the epidural catheter. Patient appraisal included demographics, assessment of vital signs, continuous pulse oximetry, and completion of a 100-mm linear VAS for pain (0 = no pain, 100 = worst pain imaginable). At the same time intervals, somnolence was assessed using a four-point ordinal scale for degree of sedation (0 = wide awake, 1 = drowsy, 2 = rousable, 3 = nonrousable), and weakness of the lower extremities was evaluated using the four-point Bromage scale. Side effects such as pruritus, nausea alone, or nausea and vomiting were also recorded at this time. The level of sensory loss to both pin prick and cold was assessed 15 min after the injection of the study solution. When the fetus was delivered or when additional epidural analgesia was given, the patient was no longer required to complete the VAS pain score. Patients were excluded from the study and considered a technical failure if satisfactory pain relief (i.e., VAS < 80) was not achieved within 20 min.

The adequacy of motor function for ambulation was assessed, using a modified Bromage scale,11 15 min after the study solution was administered. Patients were asked to demonstrate straight-leg raises, then sit at the edge of the bed, stand, and finally perform a deep knee bend at the bedside. Patients were allowed to ambulate only after they successfully demonstrated a deep knee bend and only when accompanied by a nurse.

All patients had continuous electronic FHR monitoring throughout the study period, except during periods of ambulation, when intermittent monitoring was done every half hour. Any FHR abnormalities identified by the obstetrical team were recorded. The duration of the first and second stage of labor and the requirement for an instrumented (forceps) or cesarean delivery were recorded. Patients were contacted, daily, for 5 days for evidence of a postdural puncture headache.

When patients requested additional epidural analgesia, 3 ml 1.5% lidocaine with 1:200,000 epinephrine (Astra Pharma) followed by two incremental doses of
3 ml 0.25% bupivacaine was administered. A continuous epidural infusion of 0.1% bupivacaine plus 2 μg/ml fentanyl (Janssen Pharmaceutica) was initiated at a rate of 10–14 ml/h. After the initiation of epidural analgesia, management of labor analgesia was left to the discretion of an anesthesiologist blinded to the assigned group and working on the labor and delivery service. Obstetrical management was left to the discretion of the physician (obstetrician, family physician) caring for the patient.

Data were expressed as means ± SD and were analyzed using the unpaired t test for continuous data and X² and Fisher’s exact probability test for nominal data.

### Results

Of the 39 patients enrolled in the study, 19 were assigned to the control group and 20 were assigned to the epinephrine (EPI) group. There was no significant difference between the groups as to demographic data, gestational age, cervical dilatation at the time of the intrathecal study solution was administered, and birth weight (table 1).

No technical difficulties were encountered during the establishment of the CSE in any of the patients. Cerebrospinal fluid was identified in all of the patients and was successfully aspirated after the study solution was injected.

There was no significant difference in the VAS pain scores immediately before the initiation of the CSE between the two groups. All 39 patients reported VAS pain scores of 0 within 5 min of administration of the study solutions. Seven patients (3 control, 4 EPI) delivered vaginally and two (1 control, 1 EPI) underwent cesarean delivery before requesting supplemental epidural analgesia. These patients were excluded from the subsequent analysis of VAS pain scores and determination of the duration of analgesia provided by each intrathecal study solution. Therefore, each group consisted of 15 patients for the purposes of analysis of VAS pain scores and determination of the duration of analgesia. The VAS pain scores remained 0 until 105 min in the control group and until 135 min in the EPI group after the intrathecal study solution was injected. The VAS pain scores were significantly higher in the control group between 120 min and 165 min after administering the study solution (P < 0.05; fig. 1).

The duration (means ± SD) of intrathecal labor analgesia reported in the control group was 145 ± 23 min, and in the EPI group it was 188 ± 25 min (P < 0.0001).

Ambulation was observed in 100% (19 of 19) of the control patients and in 80% (16 of 20) of the patients in the EPI group (P = NS). Of the four patients in the EPI group who did not ambulate, two demonstrated normal straight-leg raises but could not perform the required deep knee bend. The third patient could not perform a straight-leg raise due to motor weakness, and the fourth refused to ambulate because of fatigue, although she successfully demonstrated a straight-leg raise.

A similar median, range, and highest level of cutaneous sensory loss to both pin-prick and ice, in the midclavicular line, was observed with patients in both groups (table 2).

Hypotension as defined in the study design was observed in only one patient in the control group. The episode of hypotension was transient and not associated with either maternal or fetal distress. The incidence of nausea, nausea and vomiting, and pruritus was similar between the two groups after the study solutions were injected (table 2).

Three episodes of transient FHR variable decelerations were observed in each group immediately after the establishment of the CSE. All of the episodes resolved spontaneously and did not require emergent interventional delivery. Five of the six episodes were associated with rapid cervical dilatation (i.e., 3 to 10 cm in less than 2 h), and a nuchal cord was observed at the time of delivery. The sixth was associated with a concealed prolapsed cord observed during an eventual ce-
sacral delivery for arrest of decent and a nonreassuring FHR trace several hours after administration of the study solution.

There was no significant difference between the groups as to the number of participants whose labors were induced or required augmentation. The duration (means ± SD) of both the first and second stages of labor, and the time of administration of the study solution to the end of the first stage of labor also were not significantly different. The number of cesarean deliveries was similar for the two groups (table 1).

All of the patients in both groups could micturate spontaneously while under the influence of either study solution. There was no evidence of excessive somnolence or postdural puncture headaches in either group.

Table 2. Maternal Complications

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 19)</th>
<th>Epinephrine (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>1 (5.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5.2%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (5.2%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17 (90%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Treatment requested for pruritus</td>
<td>1 (5.2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Oxygen saturation &lt;95%</td>
<td>0</td>
<td>1 (5%)‡</td>
</tr>
<tr>
<td>Upper level of sensory loss to pinprick and cold at 15 min (median + range)</td>
<td>T4 (T2–T9)</td>
<td>T4 (T2–T9)</td>
</tr>
</tbody>
</table>

There are no significant differences between groups.

*By definition, transient, not associated with maternal/fetal distress.

†Patient was wide awake; transient, not associated with maternal/fetal distress.

Discussion

Herbert Braun, in 1900, first reported a prolonged anesthetic effect when epinephrine was added to intrathecal cocaine. More recently, 0.2 mg intrathecal epinephrine has been added to prolong the duration of action of local anesthetics. The addition of epinephrine to 10 μg intrathecal sufentanil, however, did not increase the duration of labor analgesia. The current investigation was undertaken to determine the efficacy of the addition of epinephrine (0.2 mg) to the combination of sufentanil (10 mg) and bupivacaine (2.5 mg) for labor analgesia.

The mean duration of labor analgesia (1-15 min) provided by the combination of 10 μg sufentanil and 2.5 mg bupivacaine was consistent with the results of the previous investigation of 148 min. The addition of 0.2 mg epinephrine to the intrathecal combination of 10 μg sufentanil and 2.5 mg bupivacaine, however, significantly prolonged labor analgesia in nulliparous patients, to a mean time of 188 min. This is the first report of an intrathecal labor analgesic combination administered to nulliparous patients with a duration of more than 3 h. There were no analgesic failures (i.e., VAS > 80) 20 min after intrathecal administration of solution in either study group, in contrast to previous reports for either sufentanil or bupivacaine alone.

The mechanism of epinephrine’s effect of prolonging the duration of labor analgesia observed in the present study is not clear. Historically, the vasoconstrictive property of epinephrine has been purported as the mechanism prolonging the effect of intrathecal local
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anesthetics. This vasoconstrictive effect presumably alters the intrathecal clearance of coadministered drugs. The effect of epinephrine on the duration of analgesia provided by 2.5 mg intrathecal bupivacaine alone for labor analgesia, however, has not been reported and requires further investigation. Alternative explanations include the possible interaction of each agent at a different spinal cord receptor site, thus resulting in an inhibition of neural excitability. Opioids, such as sufentanil, inhibit voltage-dependent calcium channels; local anesthetics, such as bupivacaine, inhibit sodium channels; and epinephrine has α2-adrenergic action. Recently, Tejwani et al. showed that bupivacaine produces a conformational change in the spinal opioid receptor that potentiates the binding of morphine. It was also shown that the α2-adrenergic receptor effect of epinephrine enhances intrathecal morphine. Thus the addition of epinephrine and bupivacaine potentially may produce further conformational changes allowing for the prolonged inhibitory effect of sufentanil at the spinal cord. Alternatively, a change may occur in the intrathecal pharmacokinetics of the coadministered agents unrelated to the vasoconstrictive properties of epinephrine. This would produce higher concentrations of one or all of the agents in the spinal cord, resulting in the observed prolongation of analgesia.

Whether the prolongation of intrathecal labor analgesia is a synergistic or additive positive interaction could not be determined by our study design and requires further investigation. Kartawidi et al. observed that the duration of intrathecal analgesia provided by the combination of 5 μg sufentanil, 1 mg bupivacaine, and 25 μg epinephrine was 137 min. This was similar to that previously reported by Campbell et al. of 148 min for 10 μg sufentanil and 2.5 mg bupivacaine. Considering the results of the current investigation, the most efficacious dose of each of the agents (sufentanil, bupivacaine, and epinephrine) when combined requires further investigation.

One of the concerns regarding the administration of local anesthetics for intrathecal labor analgesia is resultant motor blockade that may preclude ambulation. In the previous report, Campbell et al. could not detect motor blockade in any of the patients receiving the intrathecal combination of 10 μg sufentanil and 2.5 mg bupivacaine or 2.5 mg bupivacaine alone. However, that study was not specifically designed to evaluate patients' ability to ambulate. A higher, 5-mg, dose of intrathecal bupivacaine alone was reported to produce complete or nearly complete motor blockade in 40% of patients. In the present study, motor blockade also was not detected in any of the patients receiving the intrathecal combination of sufentanil and bupivacaine. All of these patients were able to ambulate. In the epinephrine group, 80% of the patients successfully ambulated. Of note, patients were only permitted to ambulate after successfully performing several maneuvers to ensure that ambulation could be safely undertaken. To detect postural hypotension, the patients were required to first sit and then stand at the bedside. To ensure adequate motor power for ambulation, each patient was required to perform a straight-leg raise, stand, and subsequently complete a deep knee bend at the bedside. Several advantages to ambulation during the first stage of labor have been suggested, including increased intensity of contractions and uterine activity with reduced requirement for augmentation, shorter duration of the first stage of labor, reduction in the incidence of instrumented deliveries, and increased patient satisfaction. Importantly, several reports, although they did not show a direct benefit of ambulation, did not report adverse effects of ambulation. Ambulation should only be attempted if there are no obstetrical contraindications; the patient is accompanied by a midwife, nurse, or physician; and there is no evidence of postural hypotension or motor blockade.

Most patients in both groups reported pruritus. Contrary to the report by Camann et al., the addition of epinephrine did not significantly reduce the incidence of pruritus. Although the doses of both sufentanil and epinephrine were similar, both groups in the present study received intrathecal bupivacaine. The difference in the results may be due to an as yet unknown interaction between sufentanil and bupivacaine at the spinal cord or higher levels that prevents the antipruritic effect of epinephrine. Most patients reported pruritus as mild, with only 10% of patients requesting and receiving treatment. Therefore, the clinical significance of the observed pruritus appears to be minimal.

The incidence of nausea and nausea plus vomiting was similar, and the clinical importance of this observation probably was minimal because most patients reported the nausea as mild.

All of the patients receiving either intrathecal study solution could void, thus avoiding intermittent or continuous bladder catheterization and its potential complications. Unfortunately, after the analgesic effect of the study solution diminished, and epidural analgesia was initiated, most of the patients required intermittent
catheterization before delivery. This inability to void was perhaps related to the concentration (0.1%) of bupivacaine in the continuous epidural infusion used in the present investigation.

This is the first report of transient FHR variable decelerations to 60 beats/min immediately after the administration of the combination of intrathecal sufentanil and bupivacaine, with or without epinephrine. None of these episodes were sustained and all resolved spontaneously within 3–4 min. The incidence of 15% in the present study is similar to that reported by Cohen et al. with intrathecal sufentanil alone. It has been suggested that an abrupt decrease in maternal plasma epinephrine levels, but not norepinephrine levels, after the administration of intrathecal sufentanil may precipitate this phenomenon. Of note, five of these FHR decelerations were associated with expedient and profound analgesia, rapid cervical dilatation (i.e., from 3 cm to fully dilated in less than 2 h), and a nuchal cord identified at the time of delivery. Therefore, these transient FHR decelerations may also be the result of a possible reduction of umbilical blood flow due to umbilical cord compression and not related to maternal plasma epinephrine levels. This mechanism requires further investigation.

One of the concerns about epidural analgesia is that it may slow the progress of labor. It was recently reported that the placement of an epidural catheter may significantly delay overall cervical dilatation from 1.18 to 0.95 cm/h. The results of the present study, however, indicate that the initiation of CSE analgesia resulted in a much faster rate of cervical dilatation rate of 1.75 cm/h for the control group and 1.41 cm/h for the EPI group. The effect the intrathecal study solutions may have on the progress of labor or labor outcome is difficult to interpret because most patients also received additional epidural analgesia before delivery. This observation requires further investigation.

It has been suggested that the motor blockade produced by epidural local anesthetics may result in laxity of the pelvic floor musculature, leading to prolonged labors and increased incidence of instrumented deliveries. Using the intrathecal solutions described in the present study, most of the parturients were able to ambulate, indicating (by extrapolation) that pelvic floor muscular tone remained intact. Whether this lack of motor blockade and the patients' ability to ambulate accounts for the shorter than predicted duration of labor observed in the present study requires further investigation.

It has also been suggested that the second stage of labor is delayed by the effects of epidural analgesia. The duration of approximately 70 min for the second stage of labor observed in the present study is much less than the 115 min reported when patients receive epidural analgesia. A recent report also suggested that the placement of an epidural catheter in nulliparous patients in labor would significantly increase the cesarean delivery rate from 2.2% to 25%. In contrast, the overall cesarean delivery rate observed in the present investigation of nulliparous women was only 10% (4 of 39). This rate of cesarean delivery closely resembles that reported by Chestnut et al. for nulliparous women undergoing spontaneous labor (i.e., 8–10%). Of note, obstetrical management (augmentation and cesarean delivery) was left completely to the discretion of the physician (perinatologist, obstetrician, or family physician) caring for the patient, none of whom were directly involved in the study or aware of the study outcomes being investigated.

In conclusion, the addition of 0.2 mg epinephrine to the intrathecal combination of 10 μg sufentanil and 2.5 mg bupivacaine substantially prolongs labor analgesia without causing clinically significant adverse maternal or fetal effects. Not only did the addition of epinephrine prolong intrathecal analgesia to more than 3 h but most patients receiving either solution could ambulate. The CSE labor analgesic technique may now provide the parturient nearly instantaneous labor pain relief lasting more than 3 h with minimal side effects.

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