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ORIGINAL ARTICLE

Intrathecal epinephrine in combined spinal-epidural analgesia for labor: dose-response relationship for epinephrine added to a local anesthetic-opioid combination

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Background: The purpose was to investigate the dose-response relationship for intrathecally administered epinephrine added to a local anesthetic-opioid combination in combined spinal-epidural analgesia for labor, in order to evaluate analgesia and side-effects.

Patients and methods: The subjects were 100 consecutive ASA I or II parturients at $\geqslant$37weeks' gestation, who received combined spinal-epidural analgesia during labor. Each woman was randomly assigned to one of five groups that received 2-mL volumes of different spinal solutions. The control group received an intrathecal injection of bupivacaine 2.5 mg and fentanyl 25 μg only. The others received epinephrine 12.5, 25, 50 or 100 μg added to this intrathecal regimen. Maternal arterial pressure, heart rate and pain scores were recorded before and 5, 10, 15 and 30 min after intrathecal injection. Level of sensory blockade, motor blockade score, duration of intrathecal analgesia, side effects, fetal heart rate, and 1- and 5-min Apgar scores were also assessed.

Results: Compared to the control group, all four epinephrine groups had significantly longer duration of intrathecal analgesia, but the durations were similar. The frequencies of side effects were similar in all five groups.

Conclusion: The results suggest that adding epinephrine to a combination of standard intrathecal doses of bupivacaine and fentanyl in combined spinal-epidural analgesia for labor significantly prolongs spinal analgesia. Of the four epinephrine doses tested, the lowest one (12.5 μg) was optimal for this clinical setting.

Keywords: Labor analgesia; Combined spinal-epidural; Epinephrine

INTRODUCTION

Intrathecal analgesia is commonly administered during the first stage of labor as part of combined spinal-epidural (CSE) technique.[1] In CSE protocols, agents are initially given intrathecally, providing profound, rapid-onset analgesia. Then additional analgesia is administered via the epidural catheter. Various drugs have been used for the intrathecal portion of CSE, ranging from opioids alone to multiple-drug combinations with local anesthetics, opioids, epinephrine, clonidine and neostigmine.[2–5] Intrathecal epinephrine doses of 25 and 200 μg have been found to prolong the duration of local anesthetic-opioid combinations given intrathecally.[6,7] However, the dose-response relationship for intrathecal epinephrine administered in CSE analgesia for labor has not been evaluated in detail. Also, the links between dosage and side effects for this epinephrine regimen are not clearly understood and the incidence of failed analgesia at different doses is not known.

Our purpose in this study was to investigate the dose-response relationship for intrathecal epinephrine added to a local anesthetic-opioid combination in CSE analgesia for labor. Special attention was focused on analgesic efficacy and incidence of side effects.

METHODS

The study was approved by our faculty ethics committee and each participant provided written informed consent.

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The subjects were 100 consecutive American Society of Anesthesiologists physical status I or II parturients. Each woman had been pregnant for at least 37 weeks and was given the study drugs while in active labor with cervical dilation less than 5 cm. Subjects were randomly assigned to one of five groups that received different hypobaric spinal anesthetic solutions, as detailed below:

- Group E0 (controls; $n = 20$): 0.5% bupivacaine 2.5 mg (0.5 mL) mixed with fentanyl 25 μg (0.5 mL) and 1 mL of distilled water
- Group E12.5 ($n = 20$): 0.5% bupivacaine 2.5 mg (0.5 mL) mixed with fentanyl 25 μg (0.5 mL) and epinephrine 12.5 μg in 1 mL of distilled water
- Group E25 ($n = 20$): 0.5% bupivacaine 2.5 mg (0.5 mL) mixed with fentanyl 25 μg (0.5 mL) and epinephrine 25 μg in 1 mL of distilled water
- Group E50 ($n = 20$): 0.5% bupivacaine 2.5 mg (0.5 mL) mixed with fentanyl 25 μg (0.5 mL) and epinephrine 50 μg in 1 mL of distilled water
- Group E100 ($n = 20$): 0.5% bupivacaine 2.5 mg (0.5 mL) mixed with fentanyl 25 μg (0.5 mL) and epinephrine 100 μg in 1 mL of distilled water.

Each individual therefore received a 2-mL total volume of solution intrathecally. The injections were aseptically prepared by an anesthesiologist who was not involved in the study, according to instructions contained in a sealed randomization envelope. The patients, investigators, obstetricians, and midwives were all blinded to group assignment.

The CSE was sited with the patient in sitting position. The skin over the injection site was infiltrated with 2 mL of 2% lidocaine, then an 18-gauge Tuohy needle was introduced at the L3-4 or L4-5 interspace. Loss of resistance to air was used to identify the epidural space, then a 27-gauge Whitacre spinal needle was passed through the epidural needle. After free-flowing cerebrospinal fluid was identified, the study solution was injected into the subarachnoid space via the spinal needle. After the spinal injection, a 20-gauge multi-orifice catheter was inserted and advanced such that there was 3 cm of catheter length within the epidural space. The patient was then moved to a supine position, taking care to avoid left uterine displacement.

Pain relief was assessed using an 10-cm visual analogue scale (VAS), with 0 indicating no pain and 10 indicating the worst pain imaginable. Duration of intrathecal analgesia was defined as the time from spinal injection of the study solution until the patient requested additional analgesia via the epidural catheter. If a patient's VAS score for pain was higher than 3, an additional 1.5 mL of 0.5% bupivacaine, fentanyl 25 μg and 0.9% saline 3 mL was administered via the epidural catheter.

Pain levels (VAS scores), heart rate and blood pressure were recorded before and 5, 10, 15, and 30 min after the intrathecal injection. Hypotension was defined as a systolic pressure <90 mmHg or 20% below baseline, and was treated with intravenous ephedrine in 5-mg increments. Oxytocin requirements and side effects, hypotension, nausea/vomiting, pruritus and motor blockade (Bromage score $\geqslant 1$; see scoring details below), were also recorded at the four post-injection time points noted above. The highest level of sensory blockade was evaluated bilaterally using pin-prick, and the maximum motor blockade score was recorded using a four-point Bromage scale (0 = no motor impairment; 1 = unable to lift the straight leg for 5 s; 2 = unable to flex the knee; 3 = unable to move the ankle joint). In each case, fetal heart rate was continuously monitored and mode of delivery (spontaneous, instrumental, cesarean) and Apgar scores at 1 and 5 min were recorded.

Statistical analysis

The Kruskal-Wallis and Mann-Whitney U tests were used to compare demographic data and group findings for duration of intrathecal analgesia, duration of delivery and cervical dilation before CSE analgesia. The Student's *t*-test was used to compare hemodynamic parameters. The Wilcoxon signed-rank test was used to compare group results for VAS scores. Group frequencies for side effects were analyzed using the χ^2 test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Table 1 shows the results for age, weight, height, parity and delivery types. The groups were comparable in all these respects. Cesarean sections were performed due to delay in labor in one case in each of groups E12.5, E25, and E100, and due to acute fetal distress in one case in each of groups E0, E25, and E100.

No technical difficulties were encountered during the CSE procedure in any of the cases. Analysis of the hemodynamic data revealed no statistically significant differences within or among the five groups with respect to mean blood pressure and mean heart rate values for the four post-injection time points assessed (5, 10, 15, and 30 min).

In each of the five groups, the mean VAS scores at all time points investigated after intrathecal injection were significantly lower than the mean pre-analgesia score ($P < 0.001$ for all time points compared to baseline in all groups) (Table 2). All the groups had similar mean VAS scores at each time point.