A Comparison of Minimum Local Anesthetic Volumes and Doses of Epidural Bupivacaine (0.125% w/v and 0.25% w/v) for Analgesia in Labor

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BACKGROUND: In this study we sought to determine and compare the minimum local anesthetic volumes (MLAV) and doses (MLAD) of two concentrations of bupivacaine for epidural pain relief in labor, and to quantify the effect on dose.

METHODS: Eighty women were randomized in a double-blind manner to receive a first bolus of either plain bupivacaine 0.125% (w/v) or 0.25% (w/v). The arbitrary starting volume was 15 mL. Subsequent volumes were decided by sequential allocation according to analgesic efficacy. A visual analog pain score ≤10 (0–100) within 30 min, indicated effective analgesia. The next woman received a decrement of 2 mL. A failure of the visual analog pain score to reach ≤10 was followed by a 2 mL increment for the next woman.

RESULTS: Using the formula of Dixon and Massey, MLAV and MLAD, with 95% confidence intervals (CI) were calculated for each concentration. MLAV was 13.6 mL (95% CI 12.4–14.8), with bupivacaine 0.125% (w/v), and 9.2 mL (95% CI 6.9–11.5) with bupivacaine 0.25% (w/v). The difference was highly significant (P = 0.002). MLAD for these volumes were 17.0 mg (95% CI 15.5–18.5), and 23.1 mg (17.2–28.9), respectively (P = 0.045).

CONCLUSIONS: Bupivacaine 0.125% (w/v) when compared with 0.25% (w/v) produced equivalent analgesia with a 50% increase in volume, but with a 25% reduction in dose. Any reduction in dose, without loss of efficacy, reduces risk of toxicity and improves safety.

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The concentration of local anesthetic injected into the epidural space that is required to block conduction of an action potential is influenced by the length of nerve root exposed to local anesthetic which, in turn, is limited by the confines of the epidural space. High concentrations of local anesthetics require only limited exposure to the nerve root, but if the pharmacological sleeve is extended to bathe all the available nerve root within the epidural space, then a lower concentration of local anesthetic will be sufficient to block nerve transmission (1).

Extending the pharmacological sleeve requires that the volume of injectate is increased at the expense of concentration. Christiaens et al. (2) showed, in a fixed dose study, that pain relief in labor was improved if the volume of local anesthetic was increased from 4 to 20 mL. Benefits have also been seen with continuous and patient-controlled epidural analgesia, again with fixed dose models (3,4). These studies show that higher volumes and lower concentrations are more effective for nerve blockade when compared with lower volumes of higher concentration local anesthetics. There are also potential benefits in differential blockade, such as motor sparing, when higher concentrations are exchanged for lower concentrations given in larger volumes.

Dose is the product of concentration and volume, and there is a potential for a reduction in dose when lower volume-higher concentration solutions are substituted with higher volume-lower concentration solutions. This reduction, however, will not be apparent when comparisons are made using a fixed-dose model. This study was therefore designed to quantify any dose reduction which might have potential implications for safety. The aim was to determine the median effective volumes and doses, which were defined as the minimum local analgesic volume (MLAV) and minimum local analgesic dose (MLAD) of bupivacaine 0.125% (w/v) and 0.25% (w/v), respectively, for epidural bupivacaine given as the first bolus to women for analgesia in labor. The two concentrations chosen for this comparison were both of a magnitude that might be expected to produce conduction blockade without any need for adjuncts.
METHODS

Patients

After hospital ethics (research) committee approval, and written informed patient consent, women in labor requesting neuraxial analgesia were recruited to this randomized, double-blind study. Only ASA physical status Class 1 or 2 patients, with a singleton pregnancy of more than 36 wk gestation, <110 kg in weight and between 150 and 180 cm in height, aged between 18 and 40 yr, with no more than 5 cm cervical dilation were considered for inclusion.

Epidural Technique

After IV access was established, the epidural space was cannulated with an 18-gauge Tuohy needle and a 20-gauge catheter, at the L2/3 or 3/4 level, in a sitting position, using a loss of resistance to saline technique. The volume of saline injected was limited to <3 mL to minimize dilution of local anesthetic (5). No epidural test dose was given. The first administration of bupivacaine was in a syringe prepared not more than 4 h previously, injected slowly over approximately 5 min. Both the woman and the observing anesthesiologist were blinded to the volume in the syringes, which were made up by another anesthesiologist with no clinical role in the study. Before inclusion, a baseline visual analog pain score (VAPS) was recorded at the height of a contraction using a 100 mm ruler, where 0 represented “no pain” and 100 “worst pain ever.”

Maternal heart rate and arterial blood pressure, uterine contractions, and fetal heart rate were monitored according to established practice.

Groups

Women were allocated to receive bupivacaine 0.125% (w/v), or bupivacaine 0.25% (w/v). The volume of local anesthetic in the first syringe of each group was arbitrarily set at 15 mL. Thereafter, the volume of solution in each individual syringe was determined by the response of the previous patient in the same group to the higher or lower volume in her test syringe, according to up-down sequential allocation. Efficacy of the first dose was assessed using a VAPS, at 0, 15, and 30 min after the injection of the test solution (first bolus). Three outcomes were possible.

Effective

Regardless of the baseline, this required that the VAPS decreased to 10 mm or less at the height of contraction within 30 min of injection, indicating the end of the study, and directed a decrement of 2 mL local anesthetic for the next woman.

Ineffective

This followed failure of the VAPS to reach 10 mm within 30 min of injection of the test solution. Rescue analgesia consisting of 12 mL bupivacaine 0.25% (w/v) was given. After this, a reduction in VAPS to 10 mm or less indicated the end of the study and directed a 2 mL increment for the next woman.

Repeat

Failure to achieve a VAPS of 10 mm after rescue directed that the same concentration be repeated for the next woman.

Each day two test syringes, rendered opaque with tape, were made up, one for each group, and placed in the refrigerator. Each syringe was labeled with a different letter from the alphabet to blind the operator to the concentration. One syringe was removed in response to a request for epidural analgesia and before recruitment. The syringes were placed side by side at the back of the refrigerator, and the operator chose one or the other at random. No further syringes were made up until the second syringe had been used. This allowed both groups to proceed at a similar pace, avoiding a terminal sequence from a single group. The investigator was not permitted to see the sequence until the end of the study. On completion of the study at 30 min, or after rescue, usual analgesic practices were followed.

Observations

For all women, age, weight, height, gestation, parity, cervical dilation, use of prostin and oxytocin infusion, VAPS, and efficacy of the local anesthetic solution were recorded.

Statistical Analysis

Personal and obstetric data were collected and presented as mean (sd) and median [interquartiles] as appropriate. The median effective local analgesic volumes and doses were estimated from the up-down sequences using the formula of Dixon and Massey (6), which enabled MLAV and MLAD with 95% confidence intervals (CI) to be derived. This analysis was backed up with Probit Regression. Analyses for group comparisons included unpaired Student’s t-test, Welch’s t-test for differing variance, Mann–Whitney U-test, and Fisher’s exact test for parametric, nonparametric, and categorical data as appropriate. The analyses were performed using Excel 2000 for Windows (Microsoft, Redmond, WA), Prism 4.0 (GraphPad Software, San Diego, CA), and Minitab 14 (Minitab, State College, PA). Statistical significance was defined for overall α error at 0.05 level with two-sided P values.

Sample Size

Sample size estimations were based on the results of the first studies that showed the minimum local analgesic concentration (MLAC) of bupivacaine to be 0.065% (sd 0.037) (7). Power was given at 0.9 with the minimum difference to be significant as a 50% difference in MLV bupivacaine. It was then estimated that a minimum of 39 women would be required per group.
Table 1. Personal and Obstetric Characteristics and Initial VAPS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bupivacaine 0.125% (w/v), N = 40</th>
<th>Bupivacaine 0.25% (w/v), N = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>25.8 (6.0)</td>
<td>26.2 (6.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (7.5)</td>
<td>165 (6.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.7 (12.7)</td>
<td>76.7 (12.4)</td>
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<td>Gestation (wk)</td>
<td>40 [39–41]</td>
<td>40 [39–40]</td>
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<tr>
<td>Nulliparous/multis</td>
<td>29/11</td>
<td>26/14</td>
</tr>
<tr>
<td>Initial VAPS</td>
<td>75 [60–90]</td>
<td>67 [61–80]</td>
</tr>
<tr>
<td>Oxytocin</td>
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<td>4</td>
</tr>
<tr>
<td>Prostin</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Results are expressed as mean (so), median [interquartile range] and count as appropriate. N = Number; VAPS = visual analogue pain score.

RESULTS

Personal and obstetric characteristics were similar for both groups (Table 1).

Eighty-seven women were recruited. Seven women failed to achieve a VAPS of 10 or less after rescue, and were withdrawn from the study. Their syringes were repeated, two in the 0.125% (w/v) group, at 11 and 15 mL, and five in the 0.25% (w/v) group, at 7 mL, 9 mL (three syringes), and 11 mL, leaving 80 women for analysis.

The sequences of effective and ineffective analgesia are shown in Figures 1 and 2. Using the up-down method of Dixon and Massey, MLAV was 13.6 mL (95% CI 12.4–14.8), with bupivacaine 0.125% (w/v), and 9.2 mL (95% CI 6.9–11.5) with bupivacaine 0.25% (w/v). This difference (95% CI 1.9–6.9) was highly significant (P = 0.002). The MLAD for these volumes were 17.0 mg (95% CI 15.5–18.5), and 23.1 mg (95% CI 17.2–28.9), respectively, the difference (95% CI 0.14–12.2) was also significant (P = 0.045). Results of the probit regression are in Table 2. The relationship of volume to dose is shown in Table 2.

DISCUSSION

We have shown that equivalent pain relief in labor can be achieved with a significant reduction in the dose of bupivacaine, when given as a bolus in a concentration of 0.125% (w/v), compared with 0.25% (w/v). The weaker concentration required a 48% (95% CI 18–87) increase in volume, but provided a 26% (95% CI 1–46) reduction in dose. Although the difference of 48% is marginally lower than the nominal 50% used for the sample size estimation, we believe that the results are important, and of interest from both a pharmacologic and a clinical perspective. Reductions in dose without loss of efficacy widen the therapeutic ratio and provide a greater margin of safety (4).

It has been suggested that the epidural volume–response curve may follow an “inverted U” relationship (7). This would be true for a fixed dose model, where minute volumes of high concentration solution move through a therapeutic range until arriving at a high volume subtherapeutic concentration (8). The nature of this sequential allocation study is that concentration was fixed, so that dose varied with volume. For a given concentration, and accepting variable dose, the volume–response curve should assume the more familiar dose–response sigmoid shape.

The volumes given to the group receiving 0.125% (w/v) exhibited tighter CIs and precision when compared with the higher 0.25% (w/v) group. CIs are influenced by variability which, in turn, is influenced by the population under study, and the chosen endpoint. A possible reason for this difference is that

Table 2. Up-Down Analysis and Probit Regression Results for Bupivacaine 0.125% (w/v) and Bupivacaine 0.25% (w/v) with 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Bupivacaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125% (w/v)</td>
<td>0.25% (w/v)</td>
</tr>
<tr>
<td>MLAV</td>
<td></td>
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<tr>
<td>Up-down analysis (mL)</td>
<td>13.6 (12.4–14.8)</td>
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<tr>
<td>Probit (mL)</td>
<td>13.5 (11.4–15.9)</td>
</tr>
<tr>
<td>MLAD</td>
<td></td>
</tr>
<tr>
<td>Up-down analysis (mg)</td>
<td>17.0 (15.5–18.5)</td>
</tr>
<tr>
<td>Probit (mg)</td>
<td>16.8 (14.2–19.9)</td>
</tr>
</tbody>
</table>

MLAV = Minimum local analgesic volume; MLAD = minimum local analgesic dose.

Figure 1. The up-down sequence is shown for bupivacaine 0.125% (w/v). Minimum local analgesic volume (MLAV) bupivacaine 0.125% (w/v) was 13.6 mL (95% CI 12.4–14.8).

Figure 2. The up-down sequence is shown for bupivacaine 0.25% (w/v). Minimum local analgesic volume (MLAV) bupivacaine 0.25% (w/v) was 9.2 mL (95% CI 6.9–11.5). The difference between the two concentrations was significant (P = 0.002).
larger volumes introduced more consistency in epidural nerve root blockade, possibly by producing a more complete pharmacological sleeve.

In choosing the two concentrations of bupivacaine for this study, there was concern as to whether the lower bupivacaine concentration, 0.125% (w/v), met our criterion that it must be capable of consistently producing effective analgesia without the need for adjuncts. Yau et al. (9) failed to achieve adequate pain relief with a bolus dose of 8 mL, and Staintorth et al. (10) found that 12 mL of plain bupivacaine 0.125% (w/v) was approximately 50% successful. The cause of failure in these studies could be blamed on inadequate volume or inadequate concentration. Failures of analgesia have also been recorded with bupivacaine 0.25% (w/v). Burke et al. (11) found that initial analgesia was inadequate in 22% of women given a 10 mL bolus of either racemic or levobupivacaine 0.25% (w/v) that included the test dose. Milligan et al. (12) observed some failures of spread with 12 mL bupivacaine 0.25% (w/v) at 30 min in obese women. The volumes of bupivacaine used in these studies are less than, or similar to, the median effective volumes that we have determined, and on the basis of our results, failures would be predictable.

We chose to include multiparous women as well as those with labors that had been induced or augmented with oxytocin. Where parity is concerned, nullipara tend to labor more slowly than multipara, and cervical dilation is a significant factor influencing MLAC (13). Parity, however, does not appear to be an independent influence as it is common for obstetric units to use the same epidural regimens for nullipara and multipara (8). Prostaglandin, which stimulates nociception, significantly increases epidural analgesic requirements (14). Provided that both groups are balanced for these factors, comparisons made should still be valid. One way to assess this is by comparing the initial VAPS. If the groups were unevenly matched, important differences in the initial VAPS would be evident.

It is possible to estimate the effective volume, EV95, from our data, but more extreme estimates lack precision when compared with the EV50 and may be inappropriate. A previous up-down study investigating the doses required to block ankle dorsiflexion ultimately included a greater number of women who were given doses that were much higher than the median value (15). The ED95 calculated from the second half of that study, and the estimated ED95 from the first were comparable (8). Because estimation of EV95 from data of this nature has its critics, we have not included EV95 estimates here. Lack of precision is not a problem with the EV50 and the median volumes we have given here. However, for the concentration studied to be effective in clinical practice, the volumes required will need to be larger than the EV50 above.

If we define dose efficiency as the lowest dose that achieves the desired effect, then it is likely that greatest efficiency should follow the use of higher volumes and lower concentrations for epidural local analgesia in the first stage of labor. Reductions in dose exposure should have implications for improving safety.

REFERENCES