Minimum Local Analgesic Dose

Effect of Different Volumes of Intrathecal Levobupivacaine in Early Labor

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Background: This double-blind, randomized study was aimed at detecting the effect of three different volumes of intrathecal levobupivacaine on the minimum local analgesic dose in early labor.

Methods: Ninety-three nulliparous women requesting combined spinal–epidural analgesia, at more than 37 weeks gestation, with spontaneous onset of labor, cervical dilatation from 2 to 5 cm, were enrolled. Parturients received 10 ml (group 10), 5 ml (group 5), or 2.5 ml (group 2.5) of the spinal solution containing plain levobupivacaine diluted with 0.9% wt/vol saline to achieve the desired dose and volume at room temperature. A lumbar epidural catheter was then placed. The initial dose for each group was 2.0 mg, and the following doses were determined by the response of the previous patient using up–down sequential allocation. The authors required the test solution to achieve a visual analog pain score of 10 mm or less to be considered effective. The up–down sequences were analyzed using the Dixon and Massey formula and regression logistic model.

Results: The minimum local analgesic dose of spinal levobupivacaine in spontaneously laboring women was 1.35 mg (95% confidence interval, 1.25–1.45 mg) in group 10, 1.65 mg (95% confidence interval, 1.51–1.76 mg) in group 5, and 1.97 mg (95% confidence interval, 1.89–2.05 mg) in group 2.5. A unit change in volume increased the odds of an effective response multiplicatively by a factor of 1.8.

Conclusions: Analgesia can be achieved using lower doses and higher volumes even in subarachnoid space. The important role of the volume should be considered not only in epidural but also in spinal analgesia.

COMBINED spinal–epidural analgesia is a popular technique and provides excellent analgesia for labor when various local anesthetics are used. Several studies suggest that the dosages of local anesthetics most extensively used are too high, and effective analgesia can be achieved with lower dosages.1–4

When performing spinal anesthesia for cesarean delivery,5,6 investigators have not always found a clinical difference when local anesthetic volumes ranging from 3 to 10 ml were injected in subarachnoid space. There is a lack of literature regarding intrathecal administration of high analgesic solution volumes for labor analgesia. Most studies report a constant volume from 2.0 to 3 ml.2,3,7–9

Levobupivacaine, the newer local anesthetic, is significantly less cardiotoxic10,11 and neurotoxic12,13 than bupivacaine and, although it is as potent as racemic bupivacaine, seems to be a more suitable agent for pain relief in laboring women.2

This study aimed at examining how different volumes of intrathecal levobupivacaine could reduce the amount of local anesthetic required in women in the first stage of spontaneous labor. Using the sequential allocation method,14 we established the median effective dose (ED50) of three different volumes of analgesic solution and defined this as the minimum local analgesic dose (MLAD) for that intrathecal volume of local anesthetic. Moreover, we were able to evaluate the levobupivacaine dose-sparing effect of large intrathecal volumes by estimating its effect on the MLAD of levobupivacaine. We found that the volume, in conjunction with other factors, had an important role in achieving complete pain relief in early labor with spinal analgesia.

Materials and Methods

After obtaining approval by the institutional ethics committee (Fatebenefratelli General Hospital, Rome, Italy) and written informed consent, 93 nulliparous women with American Society of Anesthesiologists physical status of I or II, requesting combined spinal–epidural analgesia, at more than 37 weeks gestation, with spontaneous onset of labor and cervical dilatation from 2 to 5 cm, were enrolled in our study. To prevent any interference with the study and to standardize the progression of labor, we excluded women with the presenting part below the ischial spines or with cervical dilatation in excess of 5 cm. In fact, at some point in labor, the nature of pain changes from a first-stage to a combination of first- and second-stage distribution.15

After intravenous prehydration with 500 ml lactated Ringer’s solution, the women were placed in the left lateral position, and the epidural space was identified using loss of resistance to saline at the L3–L4 intervertebral space with an 18-gauge Tuohy needle. When cerebrospinal fluid was obtained by puncturing the dura mater with a 27-gauge Whitacre spinal needle, the study drug was injected into the intrathecal space. After removing the spinal needle, a multiorifice epidural catheter was advanced 3 cm into the epidural space and aspirated. A list of discrete uniform random numbers ranging from 1 to 3 was generated, and each patient enrolled was assigned to the volume group indicated by

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Received from the Fatebenefratelli General Hospital, Rome, Italy. Submitted for publication December 27, 2004. Accepted for publication August 4, 2005. Support was provided solely from institutional and/or departmental sources.

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the list until the desired sample group size was obtained. The patients received 10 ml (group 10), 5 ml (group 5), or 2.5 ml (group 2.5) of the spinal solution from a freshly prepared syringe containing plain levobupivacaine diluted with 0.9% wt/vol saline to achieve the desired dose and volume at room temperature. The study drug was prepared by an anesthesiologist who was not involved in the parturient assessment. After catheter placement, women were turned to the supine position with a 15° left tilt and 45° elevation of the head of the bed. According to the literature and preliminary studies, the initial dose for each group was 2.0 mg, and the following doses were determined by the response of the previous woman in the same group to a higher or lower dose using an up–down sequential allocation technique. The testing increment or decrement was set as 0.1 mg. The anesthesiologist performing the procedure was not informed of the specific dose, and he could only estimate the volume injected. Subsequent assessments were registered by another anesthesiologist, who was also unaware of the dose and group allocation.

The efficacy of the study drug was assessed using a 100-mm visual analog pain score, where 0 represents no pain and 100 corresponds to the worst possible pain. Using a slide rule, with the patient’s side unmarked and the observer’s side marked from 0 to 100 mm, observations were made at time zero, defined as the end of intrathecal injection, and at 5-min intervals thereafter for the first 15 min. Three outcomes were possible:

- **Effective:** This result required a visual analog pain score of 10 mm or less within 15 min and resulted in a decrement of 0.1 mg levobupivacaine for the next woman assigned to that group.
- **Ineffective:** This result required a visual analog pain score of 10 mm or greater within 15 min and resulted in an increment of 0.1 mg levobupivacaine for the next person assigned to that group; these women received an epidural rescue bolus of 15 ml levobupivacaine, 0.125% wt/vol.
- **Repeat:** This followed if there were some problems with the combined spinal–epidural technique or a progression of labor beyond 5 cm or if the fetal head was found below the ischial spines before an outcome was reached; this result required a repetition of the same dosage for the next woman assigned to that group.

The women in whom the outcome was considered effective were asked to describe their sensations during their contractions and in their legs 30 min after the spinal injection.

Other data collected included the following:

- **Sensory block using the Hollmen scale:** grade 0 = normal puncture sensation; grade 1 = less intense puncture sensation; grade 2 = no puncture sensation but tactile sensation preserved (analgesia); grade 3 = no sensation at all (anesthesia). Sensory changes were assessed with the pinprick test using the puncture with a blunted needle. We considered that the maximum extension of sensory block was reached when the dermatome Hollmen scale at this point was registered as grade 2 (analgesia).
- **Motor block after 30 min from spinal injection using the Bromage scale:** 0 = no motor block; complete flexion of knee and foot; 1 = partial motor block; reduced flexion of knee, complete flexion of foot; 2 = almost complete motor block: no flexion of knee, flexion of foot; 3 = complete motor block: no flexion of knee, no flexion of foot.

The occurrence of any maternal side effects such as drowsiness, nausea, vomiting, and shivering were assessed as visual analog scores using a slide rule where the patient’s side was unmarked and the anesthesiologist’s side was marked from 0 to 100 mm (0 = no effect; 100 = worst effect).

Maternal pulse, arterial blood pressure, frequency of contractions, and fetal heart rate were monitored. A reduction of systolic blood pressure greater than 20% from the baseline was promptly treated with 5-mg boluses of ephedrine and was defined as a hypotension episode.

The duration of analgesia in effective cases, defined as the time between the spinal injection and when the first uncomfortable contraction was felt, was registered.

**Statistical Analysis**

The patients’ personal and obstetric data were collected and were represented as mean (SD) and median (interquartile range) as appropriate.

As a first step, we estimated the MLAD for levobupivacaine separately for the three levels of volume. Log transformations were used to normalize doses. The median effective doses of levobupivacaine were estimated from the up–down sequences using the Dixon and Massey formula for each group, and logistic regression analysis was used as a backup or sensitivity test.

Sample size estimations were based on an “average” SD for the analgesic under study (0.1 mg), used also as testing intervals in the up–down allocation. Power was given at 95% with a minimum difference of 0.3 mg and a level of significance of 0.01. We estimated that 10 women were required per group. However, because the Dixon and Massey technique requires a sample size approximately twice that number, we enrolled 31 women per group.

As a second step, we tried to analyze directly the effect of volume on the response. We put together responses coming from the three volume groups, building a regression logistic model where the dependent variable was the response (1 = effective; 0 = ineffective) and the
covariates were the analgesic dose and volume (volume–dose/response model).

Finally, to detect the effect of volume on the sensory block, we built another regression model, where the dependent variable was the sensory block and the independent variable (factor) was the volume group (volume/sensory block model).

Results

There were no significant demographic or obstetric differences among the three groups, as shown in table 1. Of the 93 women enrolled, one was rejected in each group for obstetric reasons, leaving 30 for analysis. The MLAD of the spinal levobupivacaine in spontaneously laboring women was 1.35 mg (95% confidence interval [CI], 1.25–1.45 mg) in group 10 (fig. 1A), 1.63 mg (95% CI, 1.51–1.76 mg) in group 5 (fig. 1B), and 1.97 mg (95% CI, 1.89–2.05 mg) in group 2.5 (fig. 1C), using the Dixon and Massey formula. Using logistic regression analysis as a backup testing mechanism, the results were as follows: MLAD of spinal levobupivacaine in group 10: 1.28 mg (95% CI, 1.2–1.4 mg); MLAD in group 5: 1.57 mg (95% CI, 1.5–1.6 mg); MLAD in group 2.5: 1.98 mg (95% CI, 1.90–2.0 mg). We obtained significant differences for ED50 for the three levels of volume; all differences were greater than 0.3 mg (table 2).

Using the volume–dose/response model described above, we found that the effect of a unit change in volume (1 ml), with the dose remaining fixed, increased the odds of an effective response multiplicatively by a factor of 1.8. Overall, 70% of the women’s responses were correctly classified by this model.

A significant effect of volume on sensory block resulted from the volume/sensory block model. The effect of a volume group change increased the height of sensory block by a factor of 2.14.

Values are presented as mean ± SD.

\* P < 0.029 vs. group 10. † Results are expressed as median (interquartile range); the effect of a volume group change increases the height of sensory block by a factor of 2.14 (P < 0.001).

VAPS = visual analog pain score.

Table 1. Demographic and Obstetric Data and Duration and Maximum Height of Sensory Block for Women with Effective Analgesia

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Gestational age, weeks</th>
<th>Cervical dilatation, cm</th>
<th>Initial VAPS, mm</th>
<th>Duration analgesia, min</th>
<th>Sensory block†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>31.7 ± 3.7</td>
<td>71.9 ± 6.9</td>
<td>39.5 ± 1.0</td>
<td>3.7 ± 0.8</td>
<td>96.5 ± 6.7</td>
<td>91.1 ± 12.4</td>
<td>T9 (T9–T8)</td>
</tr>
<tr>
<td>5</td>
<td>31.4 ± 3.8</td>
<td>72.5 ± 12.1</td>
<td>39.7 ± 1.19</td>
<td>3.5 ± 1.02</td>
<td>92.8 ± 9.7</td>
<td>80.44 ± 29.6</td>
<td>T7 (T7–T7)</td>
</tr>
<tr>
<td>10</td>
<td>31.1 ± 5.2</td>
<td>69.4 ± 6.6</td>
<td>39.7 ± 0.9</td>
<td>3.8 ± 0.9</td>
<td>89.8 ± 12.2</td>
<td>66.8 ± 15.6</td>
<td>T4 (T5–T4)</td>
</tr>
</tbody>
</table>

Table 2. MLAD of Levobupivacaine in Different Intrathecal Volumes with 95% CIs

<table>
<thead>
<tr>
<th>Group</th>
<th>MLAD (95% CI), mg</th>
<th>Logistic Regression (95% CI), mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>1.97 (1.89–2.05)*</td>
<td>1.98 (1.90–2.0)</td>
</tr>
<tr>
<td>5</td>
<td>1.63 (1.51–1.76)†</td>
<td>1.57 (1.5–1.6)</td>
</tr>
<tr>
<td>10</td>
<td>1.35 (1.25–1.45)</td>
<td>1.28 (1.2–1.4)</td>
</tr>
</tbody>
</table>

All differences among groups were greater than 0.3 mg.

\* P < 0.05 vs. group 5 and group 10. † P < 0.05 vs. group 10.

CI = confidence interval; MLAD = minimum local analgesic dose.
Thirty minutes after the intrathecal injection, all subjects with an effective result in group 5 and group 10 had a Bromage scale score of 0, whereas 9 women (53.5%) in group 2.5 showed a Bromage scale score of 1.

The maximum extension of the sensory block was observed 15 min after intrathecal injection and was T4 (T5–T4) in group 10, T7 (T7–T7) in group 5, and T9 (T9–T8) in group 2.5.

No patients had any side effects such as nausea, vomiting, tinnitus, or shivering.

Hypotension occurred in 46.7% of effective cases in group 2.5, but there was no evidence of this side effect in group 5 and group 10.

“Tingling legs” were reported by 46.7% of women with an effective result in group 2.5 but none in group 10 or group 5. All women in group 5 and group 10 were able to refer positively to their ability to feel contractions but described the same as painless. No women in group 2.5 commented on their contraction sensations.

Discussion

We established the MLAD of three different volumes of intrathecal levobupivacaine in the first stage of labor. We demonstrated a volume-dependent reduction in levobupivacaine requirements on establishing the MLAD. In a recent study, the minimum local analgesic dose of intrathecal levobupivacaine has been suggested to be 2.95 mg; this result was obtained with an analgesic solution of 2.5 ml, and it seems relatively high if we focus on the first stage of labor. 19 Even the dosages proposed by other authors for pain relief in labor spinal analgesia were higher with respect to our findings. Perhaps if we reflect on intrathecal drug administration in terms of concentration and not only in terms of dosage, we might achieve the effective analgesia using lower doses and higher volumes even in the subarachnoid space during the first stage of labor.

We found that the effect of a 1-ml change in volume, with the dose remaining unchanged, increased the odds of an effective response multiplicatively by a factor of 1.8. The decrease of the MLAD of local anesthetic when the volume of analgesic solution increases is likely due to a more differential nerve block. Other studies did not confirm our results because they investigated the volume in spinal anesthesia and not in spinal analgesia. 20,21 They concluded that the absolute dose is more important than either volume or concentration of local anesthetic to obtain adequate anesthesia. Our goal was to obtain the most effective spinal analgesia with the optimal side effect profile; these benefits could be achieved by the selective block of C fibers.

The C fibers are predominantly involved during the first stage of labor. 22,23 We can suppose that with a more diluted analgesic solution, we would obtain a more differential sensory block between C fibers and Aδ, which are myelinated, are larger, are recruited as labor progresses, and require more local anesthetic to be blocked. 24 This could explain the significant effect of a volume group change in increasing the height of sensory block by a factor of 2.14. We could achieve the sensory block at T4 with 10 ml of study solution, blocking a greater number of C fibers.

We can thus speculate that in the earliest stage of labor, we have blocked only the smallest and nonmyelinated C fibers, without any or with undetectable effects on the other fibers. In fact, we may have saved A fibers, which have a diameter greater than C fibers, because no hypotension episodes occurred in effective cases in group 10 and group 5, but episodes did occur in 46.7% of the effective cases in group 2.5, as confirmed by other authors, who suggested that when the analgesic solution concentration decreases, the drug concentration penetrating the nerves is reduced and the sympathetic block can be less intense. 21 We might affirm that we saved Aγ fibers because none of the women with an effective result in group 10 and group 5 reported tingling legs, but 40% of women with an effective result in group 2.5 reported that their legs did not feel normal. Women with an effective result in group 5 and group 10 were also all able to distinguish uterine contractions as painless and described them as “something contracting from the upper to lower abdomen.” 25 Even this result could be due to a preferential block of C fibers.

We speculate that if we inject more and more diluted solutions into subarachnoid space, we may obtain a better dissociation even between sensory and motor block. This would explain why we found no motor block in group 5 and group 10 (women were able to stand up and walk without any help and were able to bend their knees in the orthostatic position), but we found 53.5% of the women with an effective result in group 2.5 with a Bromage score of 1. This has also been confirmed by other anatomical findings 26 that could justify the decrease of motor block to a smaller penetration of local anesthetic in ventral roots if the concentration of analgesic solution decreased.

In group 10, the higher volume produced a shorter duration of analgesia (66.6 min) with respect to group 2.5 (91.1 min). This result was statistically significant and might be due to a more concentrated local anesthetic. When the fetal head descends with the progression of labor, the larger Aδ sensory fibers, which are more and more recruited as labor progresses, remain blocked. During the first stage of labor, a profound sensory block is not required. However, in group 5, pain reoccurred after 80.44 min, and if we consider the SD, we might affirm that the higher volume does influence the duration, but with an acceptable reduction. In fact, this duration was similar to that of the intrathecal regimens currently used in clinical practice. 27 Moreover, the duration is only important if this is not combined with epidural analgesia.

Anesthesiology, V 103, No 6, Dec 2005

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for additional analgesia. Many obstetric anesthesiologists are used to starting an epidural infusion soon after the spinal injection rather than waiting until pain returns; this would decrease the clinical significance of the decreased duration with higher volumes.

The differential block we obtained in the larger volume groups is desirable because the analgesia is excellent and the side effect profile is enhanced. Our precise objective was to estimate ED₅₀ and not ED₉₅, which, however, we did estimate but did not report in the text because we considered that, even if clinically more relevant, it was more difficult to estimate precisely with the chosen method. However, we believe that using ED₅₀ to demonstrate volume group differences raises the definite possibility that similar behaviors may occur at ED₉₅ doses that are what clinical care demands. Our findings suggest that further studies must be conducted on the effects of dilute volume on the clinical properties of spinal analgesia.

References

5. Van Zundert AA, De Wolf AM, Vaes L, Soetens M. High volume spinal anesthesia with bupivacaine 0.125% for cesarean section. ANESTHESIOLOGY 1988; 69:998–1003