Predictors of Increase of Sensory Blockade

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Background: Extension of sensory blockade after an epidural top-up in combined spinal epidural (CSE) anesthesia is partly attributed to compression of the dural sac by the injected volume. This study investigated whether a volume effect plays a significant role when administering an epidural top-up after an initial epidural loading dose and assessed the predictive value of different factors with respect to the increase in sensory blockade.

Methods: After an epidural loading dose of 75 mg ropivacaine, 0.75%, 30 patients were randomly assigned to one of three groups. After the maximum level of sensory blockade (MLSB) had been established, patients received either an epidural top-up with 10 ml ropivacaine, 0.75% (group 1, n = 10) or saline (group 2, n = 10), or no epidural top-up (group 3, n = 10). Subsequently, sensory blockade was assessed at 5-min intervals for a further 30 min by a blinded observer.

Results: The MLSB increased significantly in the patients receiving an epidural top-up with ropivacaine but not in the patients receiving normal saline. Sensory block extension was inversely related to the number of segments blocked at the time of the epidural top-up, and female gender was associated with a smaller increase in MLSB.

Conclusions: When using epidural ropivacaine, the extension of sensory blockade after administering an epidural top-up is caused by a local anesthetic effect and not by a volume effect. Under the conditions of this study, predictors of the increase in sensory blockade are the presence of ropivacaine in the top-up injectate, the number of segments blocked at the time of epidural top-up, and gender.

以来 Curbelo1 described the introduction of a ureteral catheter into the lumbar epidural space, continuous epidural anesthesia (CEA) has become one of the cornerstones of modern anesthesia. Either as a single technique or in combination with spinal anesthesia (combined spinal epidural, CSE) or general anesthesia, CEA is used for operative procedures in everyday practice.

In CSE, it has been demonstrated that the increase in the maximum level of sensory blockade (MLSB) after an epidural top-up can be partly attributed to a volume effect because the volume of the fluid injected into the epidural space compresses the dural sac and causes a cephalad spread of local anesthetic already present within the cerebrospinal fluid (CSF).2–4 Another factor that contributes to the extension of sensory blockade after an epidural top-up in CSE is the dose of the local anesthetic. In analogy, it may be speculated that the same mechanisms apply when administering an epidural top-up after an initial epidural loading dose. After an epidural loading dose, local anesthetic appears in the CSF, possibly in a sufficient amount to mimic the volume extension of sensory blockade seen with an epidural top-up in CSE. We performed a randomized, double-blinded, placebo-controlled trial to test this hypothesis and to assess the relative contribution of different factors to the extension of sensory blockade after administration of an epidural top-up.

Materials and Methods

We studied 30 patients (aged 18–80 yr, American Society of Anesthesiologists [ASA] physical status I–III; nonpregnant) scheduled for lower limb surgery with lumbar epidural anesthesia. The study protocol was approved by the local ethics committee of the Leiden University Medical Center, and informed consent was obtained from all patients. The patients were randomly allocated to one of three groups of 10 patients each using a computer-generated randomization list. Premedication consisted of 7.5–15 mg (dose based on patient’s age and physical condition) of midazolam orally 1 h before regional anesthesia was initiated. Standard monitoring (continuous electrocardiograph [ECG], peripheral oxygen saturation, and noninvasive oscillometric blood pressure measurements at 5-min intervals) was applied throughout the study.

Epidural anesthesia was performed with the patient in the sitting position. A 17-gauge Tuohy needle (Becton Dickinson, Franklin Lakes, NJ) was introduced at the third lumbar interspace. In all patients, the epidural space was identified via a paramedian approach using loss of resistance to saline. Care was taken to limit the volume of saline injected on entry into the epidural space to less than 1 ml. After a negative aspiration test, the patients received an epidural loading dose of 10 ml ropivacaine, 0.75%, in 20 s, and the time was designated t = 0 (first phase). A 19-gauge multiorifice catheter was
then introduced 5 cm into the epidural space, and the epidural needle was subsequently removed. The patient was then placed in the supine horizontal position for the entire study period.

The upper level of sensory block was measured every 5 min by an independent blinded observer who determined the loss of temperature sensation in the anterior axillary line using an ice cube. The highest segment at which the patient was not capable of detecting the cold temperature of the ice cube was recorded. Establishment of the MLSB was defined as no further increase during three consecutive measurements and more than 20 min after epidural injection. The onset time to MLSB was defined as the time from epidural injection to the time when the MLSB was first recorded.

If the MLSB reached T3 or above, the patient was not included in the study; no epidural top-up was given; and the corresponding envelope remained sealed. After achieving MLSB at or below T4, the patient was included in the study, and the observer assessing sensory blockade left the room. Patients in group 1 received an epidural top-up with 10 ml ropivacaine, 0.75%; patients in group 2 received an epidural top-up with 10 ml normal saline; patients in group 3 received no epidural top-up. Patients in groups 1 and 2 were blinded to the epidural injection given. Patients in group 3 were told that an epidural injection was made while the epidural catheter was manipulated. The epidural top-up was given by one of the authors not involved in the assessment of sensory and motor block. After completing the real or simulated epidural injection, time was again designated as \( t = 0 \) (second phase). The observer measuring sensory blockade then returned to continue assessing sensory blockade at 5-min intervals for a further 30 min. Onset and MLSB during the second phase were determined according to the definitions described for the first phase. The study was concluded at the end of this observation period, and the epidural catheter was used for intraoperative top-ups or postoperative analgesia as deemed necessary by the attending anesthesiologist. All data were collected before surgery, i.e., surgery did not start until the second phase had been completed.

### Statistical Analysis

Sample size calculations showed that at least eight patients per group were required to detect an increase of at least two segments in the MLSB with a power of 80% (two-tailed \( \alpha = 0.05 \)). Data on patient characteristics are expressed as mean \( \pm \) SD. Intergroup comparisons regarding patient characteristics were made using one-way analysis of variance (ANOVA) or the chi-square test, as appropriate. The time to onset of MLSB is expressed as mean \( \pm \) SD. Data on the MLSB and segmental increase are presented as median (range). The increase in MLSB during the second phase (i.e., after the real or simulated epidural top-up) was initially assessed by a one-way ANOVA followed by Newman–Keuls test. In addition, a prognostic model exploring the additional prognostic value of various covariates was developed.

Besides the intervention (top-up with either ropivacaine or saline, or nothing), age, height, weight, lean body mass (LBM), body surface area (BSA), gender, and the maximum number of segments blocked (MNSB = number of segments counted from S5 upward to and including MLSB) of the first phase were taken as possible prognostic variables. The association between each prognostic variable and increase in MNSB was quantified using univariate linear regression analysis (SPSS, release 9.0). (SPSS Inc., Chicago, IL). Significantly associated variables (based on Student \( t \) test with \( P \) value \( \leq 0.05 \)) were evaluated, in addition to the intervention, by multivariate linear regression modeling to determine their independent contribution to the increase in level of MLSB. A significant partial F test \( (P < 0.05) \) dictated the inclusion of a determinant as a significant prognostic determinant in the model, in addition to the intervention. Interaction of biologically plausible combinations of the intervention and other determinants, or of determinants with each other, were tested by the partial F test. A significant partial F test \( (P < 0.05) \) for a model containing the interaction term compared with the model without the interaction resulted in inclusion of the term in the model.

### Results

To randomize the required 30 patients, 48 patients had to participate in the study. In 18 patients, the MLSB (first phase) reached T3 or higher, and consequently these patients were not randomized.

There were no significant differences among the three groups regarding age, height, or weight (table 1). Data on onset times, MLSB, and segmental increase are presented in table 2. A graphical representation of the segmental increase after the real or simulated epidural top-up is shown in figure 1.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 10)</th>
<th>Group 3 (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 ( \pm ) 17</td>
<td>49 ( \pm ) 16</td>
<td>51 ( \pm ) 12</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177 ( \pm ) 8</td>
<td>179 ( \pm ) 9</td>
<td>173 ( \pm ) 6</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 ( \pm ) 13</td>
<td>84 ( \pm ) 14</td>
<td>85 ( \pm ) 10</td>
<td>NS</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/3</td>
<td>8/2</td>
<td>8/2</td>
<td>NS</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>58.3 ( \pm ) 6.3</td>
<td>62.8 ( \pm ) 10.0</td>
<td>60.3 ( \pm ) 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ( \pm ) 0.1</td>
<td>2.0 ( \pm ) 0.2</td>
<td>2.0 ( \pm ) 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean \( \pm \) SD.

*Group 1 = epidural top-up with 10 ml ropivacaine, 0.75%; group 2 = epidural top-up with 10 ml normal saline; group 3 = no epidural top-up; NS = not significant.*

\[ \text{LBM} = \text{lean body mass; } \text{LBM (men)} = 1.1 \times \text{weight} - 128 \times (\text{weight/height})^2; \]
\[ \text{LBM (women)} = 1.07 \times \text{weight} - 148 \times (\text{weight/height})^2. \]

\[ \text{BSA} = \text{body surface area} = \text{weight}^{0.425} \times (\text{height})^{0.725} \times 0.007184. \]
Table 2. Maximum Levels of Sensory Blockade and Onset Times

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 10)</th>
<th>Group 3 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum sensory level</td>
<td>Onset time (min)</td>
<td>Maximum sensory level</td>
</tr>
<tr>
<td>Phase 1</td>
<td>T10 (T5–S1)</td>
<td>14 ± 7.0</td>
<td>T9 (T5–L1)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>T6 (T3–T11)</td>
<td>15 ± 5.5</td>
<td>T7.5 (T4–L1)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or median (range). Groups are defined in Table 1.

Analysis of variance of the segmental increase in the MLSB during the second phase between the three groups showed a significant difference; post hoc testing using Newman–Keuls test showed a significant difference between group 1 and group 2 (P < 0.001) and between group 1 and group 3 (P < 0.001).

In addition to the intervention, the exploratory prognostic model included two determinants independently and significantly predicting the increase (in number of sensory segments) of the MLSB, namely, the MNSB after the initial epidural loading dose of 10 ml ropivacaine, 0.75%, and gender (table 3).

The exploratory prognostic model, predicting the increase in maximum level of sensory blockade after an intervention, is: Increase of MLSB (number of segment) = \( \beta_0 + (\beta_1 \times \text{MNSB phase 1}) + (\beta_2 \times \text{Gender}) \), where \( \beta_0 \) is a constant, \( \beta_1 \) a parameter that varies with the intervention, and gender = 0 for male subjects and 1 for female subjects. Three patients receiving no epidural top-up (group 3) showed an increase in the MLSB of one segment, and this result accounts for the constant \( \beta_0 \) in the model.

Obviously, the increase of the MLSB was determined by the intervention. A top-up of 10 ml of ropivacaine, 0.75%, accounted for the largest increase in the MLSB and did so significantly compared with no epidural top-up. A top-up with normal saline increased the MLSB to a lesser extent and not significantly.

A second independent predictor of the increase in the MLSB was the initial MNSB (phase 1): the higher the initial MNSB, the smaller the increase in the MLSB after the intervention.

The third independent predictor was gender: after an intervention, the increase in the MLSB in women was smaller than in men. We evaluated whether this difference in gender was related to age, weight, or height. However, the partial Scheffé F test was not significant for any of the interaction terms. Thus, although gender was a significant predictor of the increase in the MLSB after an intervention, no effect modification of gender could be demonstrated.

Surgery was completed with epidural anesthesia in all patients. Anesthesia was adequate, with none of the patients requiring general anesthesia or intravenous opioid supplementation. Because of a delay between the time of administration of the epidural loading dose and the beginning of surgery, some of the patients in the control group received an epidural top-up with ropivacaine, 0.75%, after completion of the study period.

Table 3. Exploratory Prognostic Model Predicting the Increase in Number of Segments after Initial Bolus, followed by Either Top-up of Ropivacaine, Saline, or Nothing

<table>
<thead>
<tr>
<th>Coefficient (SE)</th>
<th>t test (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant ( \beta_0 ) = 2.89 (1.12)</td>
<td>2.59 (0.02)</td>
</tr>
<tr>
<td>Group 1 ( \beta_1 ) = 3.347 (0.537)</td>
<td>6.23 (&lt;0.0005)</td>
</tr>
<tr>
<td>Group 2 ( \beta_1 ) = 0.529 (0.496)</td>
<td>1.07 (0.29)</td>
</tr>
<tr>
<td>Group 3 ( \beta_1 ) = 0</td>
<td>0</td>
</tr>
<tr>
<td>MNSB first phase ( \beta_2 ) = -0.16 (0.07)</td>
<td>-2.22 (0.04)</td>
</tr>
<tr>
<td>Gender ( \beta_3 ) = -0.978 (0.491)</td>
<td>-1.89 (0.05)</td>
</tr>
</tbody>
</table>

Intervention group 1 = epidural top-up with 10 ml ropivacaine 0.75%; Intervention group 2 = epidural top-up with 10 ml normal saline; Intervention group 3 = no epidural top-up given. MNSB first phase = maximum number of segments blocked after the initial bolus of ropivacaine 0.75%.

Gender: 0 = male; 1 = female.

Model: increase of MLSB (number of segments) = \( \beta_0 + \beta_1 + (\beta_2 \times \text{MNSB phase 1}) + (\beta_3 \times \text{Gender}) \).

Fig. 1. Individual data on the maximum level of sensory blockade (MLSB) during phase 1 (●) and phase 2 (●). The horizontal axis represents individual patients, and the vertical axis represents the dermatomal level.
Discussion

The mechanism of action of epidural anesthesia has been reviewed elsewhere.\textsuperscript{2,3} It is generally assumed that the spinal roots in the epidural space are the principal site of action of an epidurally administered loading dose of local anesthetic. After an epidural loading dose, local anesthetic appears in the CSF, presumably by diffusion through the dural sleeves that cover the spinal roots. However, this process takes time, and although a local anesthetic concentration will build up in the subarachnoid space over time, it seems unlikely that a subarachnoid site of action of local anesthetic contributes significantly in establishing sensory blockade after an initial epidural loading dose. On the other hand, when administering an epidural top-up, the extension of sensory blockade is rapid, and this phenomenon has been attributed to the presence of local anesthetic in the CSF as a result of the initial epidural loading dose.\textsuperscript{2,3}

In our study, we observed a significant increase in the MLSB after an epidural top-up with ropivacaine. Although some of the patients in the group receiving epidural saline showed an increase, this finding was statistically not significant, and a volume effect (resulting from dural sac compression) could not be demonstrated. This result contrasts with CSE anesthesia, where previous studies\textsuperscript{7–9} have shown that the increase in the MLSB after an epidural top-up can be partly attributed to a local anesthetic effect and partly to a volume effect.

One explanation for several patients in the saline group not responding to the epidural top-up might be catheter malposition; however, we consider this unlikely for two reasons. First, in all patients in whom the epidural catheter was used after completion of the study, the catheter functioned properly. Second, because all patients receiving an epidural top-up with ropivacaine responded with an increase in the MLSB, it would be highly coincidental for any catheter malpositions to have been concentrated in the group receiving an epidural top-up with saline.

Assuming that ropivacaine injected into the epidural space will appear in the CSF, there is a possibility that compression of the dural sac by a subsequent epidural fluid injection will increase the MLSB by a volume effect, as has been demonstrated in CSE. However, it is obvious that the amount of ropivacaine present in the CSF is the critical factor determining whether this is going to happen. Our data suggest that after an epidural loading dose, the resulting CSF concentration of ropivacaine at the time that the MLSB is established is insufficient to contribute to block extension by means of a volume effect when an epidural top-up is administered. This finding may be explained on a pharmacokinetic basis, where it may be speculated that the balance between distribution of ropivacaine from the epidural to the subarachnoid space and the speed of absorption of ropivacaine from the CSF prevents the build up of a concentration sufficient to allow a volume effect. Alternatively, the initial vascular absorption of ropivacaine from the epidural space may be too extensive to allow for significant transfer from the epidural to the subarachnoid space. Whether this phenomenon would apply for all local anesthetics or whether it is drug related is a question that remains to be answered. Lastly, because our sample size was relatively small, the possibility of a type II error must be considered.

When the MLSB has been established according to our criteria, it is still possible that sensory blockade will increase further and that the conclusion of established MLSB has been drawn prematurely. For this reason, we included a control group, to whom no epidural top-up was given. A second reason to include a control group was to compensate for investigator bias. In this control group, an increase of one dermatome was found in three patients; the remaining seven patients showed no increase.

Our data show that the initial MLSB after an epidural loading dose is an important determinant of sensory block extension after an epidural top-up. The higher the initial MLSB is, the smaller the increase in dermatomal segments after the epidural top-up. In the subarachnoid space, the concentration of local anesthetic will decrease in a cranial direction. Although speculative, it is conceivable that a low MLSB is associated with a larger area of CSF containing “subclinical” concentrations of local anesthetic cranial to the spinal segment corresponding with the MLSB dermatome. This result would cause a larger extension when administering the second dose of local anesthetic.

Gender also is a significant predictor, the increase in the MLSB after an epidural top-up being smaller in women. As this difference is not related to other factors such as height or weight, the reason for this finding remains speculative.

A surprising finding was that the initial MLSB after a loading dose of 10 ml of ropivacaine, 0.75%, was on the average much higher than expected. Eighteen patients could not be included because the MLSB extended to T3 or higher after the epidural loading dose.

In conclusion, this study shows that when using ropivacaine, 0.75%, for epidural anesthesia, an epidural top-up with ropivacaine and not saline results in a significant increase in the MLSB, indicating that under these conditions a volume effect plays no role in the extension of sensory blockade. The number of segments blocked at the time of administration of the epidural top-up and female gender are predictors of the extension of sensory blockade, the former being inversely related to sensory block extension and the latter being associated with a smaller increase.
References