Comparison of 2 concentrations of levobupivacaine in postoperative patient-controlled epidural analgesia

Mira Dernedde MD (Staff Anesthesiologist)*, Michaela Stadler MD, MSc (Staff Anesthesiologist, Director Acute Pain Service), Françoise Bardiau RN, PhD (Associate Professor, Assistant Director of Nursing), Jean G. Boogaerts MD, PhD (Professor, Chairman)

Department of Anesthesiology, University Hospital Center, 6000 Charleroi, Belgium

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Abstract

Study objectives: To evaluate the quality of analgesia and the incidence of side effects of 2 different concentrations of levobupivacaine given as an equal milligram–bolus dose (5 mg) via patient-controlled epidural analgesia after abdominal surgery.

Design: Prospective, randomized, blinded study.

Setting: Postanesthesia care unit and surgical wards of a university hospital.

Patients: Forty-nine patients (41 with complete file) undergoing major lower abdominal surgery.

Interventions: The patients were randomly assigned to 2 groups: 1.5 mg/mL (bolus 3.3 mL, lockout 20 minutes, n = 26) and 5 mg/mL (bolus 1 mL, lockout 20 minutes, n = 23). The epidural catheter was inserted in the low thoracic level (T9-T12) before induction of a standardized general anesthesia technique.

Measurements: Demography, upper sensory block, visual analog scale scores at rest and after coughing, levobupivacaine and rescue morphine consumption, motor blockade, hemodynamics, postoperative nausea and vomiting, sedation, and patient satisfaction were recorded within the first 48 hours.

Main results: Both groups were similar with regard to demographics, upper level of sensory blockade (T8), and visual analog scale pain scores at rest and after coughing, as well as levobupivacaine and subcutaneous rescue morphine consumption. Motor blockade in the lower limbs was very low in both groups. Arterial blood pressure was slightly lower in the 5 mg/mL group during the first 24 hours (P = 0.052). Five patients in the 1.5 mg/mL and 7 in the 5 mg/mL group had postoperative nausea and vomiting (P = 0.43). No other side effects were recorded, and all of the patients were satisfied.
1. Introduction

The relative effects of mass, volume, and concentration of local anesthetic solutions used for epidural anesthesia and analgesia are still subject of debate. In clinical studies [1-5], contradictory results have been reported, probably due to the fact that the total dose of local anesthetic was not taken into consideration. Bromage [6] found that it is the total local anesthetic dose, and not the total volume, which determines the spread and quality of analgesia. Others have confirmed this finding, after both lumbar [7] and midthoracic [8] epidural administration. Nevertheless, it remains unclear in the literature whether the concentration influences the quality of pain relief during epidural analgesia when the total dose is held constant [9-11]. For continuous thoracic epidural administration, Dernedde et al [12,13] demonstrated that a high-concentration/low-volume local anesthetic infusion provided an equal quality of postoperative analgesia as a low-concentration/high-volume infusion and induced less motor blockade as well as less hemodynamic repercussions.

In patient-controlled epidural analgesia (PCEA), to date, only 2 studies have evaluated the influence of volume and concentration of the local anesthetic [14,15]. Both studies highlighted that the quality of analgesia was comparable with either low or high concentrations of the local anesthetic, but with reduced motor blockade [14] and drug consumption [15] using a low-concentration/high-volume approach.

Based on our previous results with continuous thoracic epidural administration of local anesthetics, we designed a prospective, randomized, double-blind study to compare 2 different concentrations of levobupivacaine, 1.5 and 5 mg/mL, given in equal total milligram–bolus doses (ie, 5 mg), via PCEA mode after lower abdominal surgery.

2. Materials and methods

After approval by the University Hospital Center Ethics Committee, written informed consent was obtained from 49 consecutive American Society of Anesthesiologists physical status I, II, and III patients undergoing elective lower abdominal surgery. Patients were enrolled in the study if they were between 18 and 75 years old, were able to read and understand French, had normal mental health, and were being hospitalized for elective surgery. Exclusion criteria were sepsis, allergy to amide-type local anesthetics or morphine, and coagulopathy. At the time of the preoperative visit, patients were familiarized with a 10-cm visual analog scale (VAS) device for pain (0 = no pain at all, 10 = worst imaginable pain) and nausea [16] intensity assessment (0 = no nausea at all, 10 = worst imaginable nausea).

Patients were premedicated with either midazolam 3 to 6 mg administered intramuscularly 1 hour before induction of anesthesia or with alprazolam 0.5 to 0.75 mg orally in the morning of the intervention. In the operating room, after infusion of 500 mL Ringer solution via an intravenous (IV) cannula, a 20-gauge epidural catheter was inserted through an 18-gauge Tuohy needle into the epidural space at a low thoracic level. The epidural catheter was directed cephalad for a distance of 4 cm and fixed to the back of the patient. As soon as the patient was in the supine position, a test dose of 3 mL 5 mg/mL levobupivacaine (Chirocaine, Abbott, Belgium) was injected to exclude subarachnoid positioning of the catheter as proposed by Murdoch et al [17] and Daoud et al [18].

Standardized general anesthesia was maintained with sevoflurane in 50% oxygen in air or nitrous oxide associated with sufentanil and myorelaxant. Based on an antiemetic institutional policy [19], 2 mg tropisetron (Novaban, Novartis, Belgium) was administered to all patients. Three to 6 mL of 5 mg/mL levobupivacaine was injected through the epidural catheter for the surgical procedure. If surgery lasted longer than 2 hours, patients received an additional injection of half of the original volume of the local anesthetic using the same concentration. After completion of the operation and tracheal extubation, patients were transferred to the postanesthesia care unit where they remained under constant observation for approximately 4 hours. The patients received, in a random fashion using a computer-generated randomization schedule, either 1.5 mg/mL levobupivacaine as a 3.3-mL bolus on demand, with a lockout interval of 20 minutes (n = 26), or 5 mg/mL levobupivacaine as a 1-mL bolus on demand, with a similar lockout interval (n = 23) via a PCEA pump (Abbott aim plus, Abbott Laboratories, North Chicago, III). No additional bolus injections were allowed. Patients received multimodal analgesia consisting of every 6-hour IV propacetamol (2 g) and ketorolac (60 mg daily) for postoperative pain relief. Rescue medication with morphine was provided via subcutaneous injections after each 4-hour evaluation of the VAS scale. Subcutaneous morphine consumption during the 48-hour study period was recorded by the nurses who administered the drug. After 48 hours, PCEA was discontinued, and alternative analgesia was provided.

On arrival in the postanesthesia care unit, patients were asked to rate their pain experience on the VAS device. This process was repeated every 2 hours for the first 4 hours and continued every 4 hours for 48 hours after the patient was
2.1. Statistical analysis

Results were expressed as means ± SD for quantitative variables and as frequencies for categorical findings. Time-related VAS measurements were summarized using different pain indicators as described elsewhere [12,13,20]: AUC, area under the VAS-time curve (cm²); mean VAS (cm); VASmax, peak of VAS (cm); Tmax, time of VASmax (hour); PVAS >3, the persistence of VAS more than 3 cm (ie, the period during which VAS was more than the critical threshold [hour]); and Pdur, pain duration (ie, the period during which the patient reported pain [VAS >0]) over the 48 hours (hours). The comparison of mean values was done by Wilcoxon test, whereas proportions were compared by the classical χ² test. The general linear mixed model (GLMM) was used to analyze repeated measures of continuous data. The GLMM tests 2 null hypotheses as follows: (1) time has no effect on the variable, which means that the variable mean of the combined groups does not vary over time, and (2) the time patterns are equal between the 2 groups, which means that the difference between the mean of each group is the same at every time point. The Bonferroni test, based on Student t statistic, was used for post hoc testing. The number of patients included in the study was based on our previous results and on a power calculation assuming a 20% difference with α = .05 and β = .20 [12,13]. All statistical calculations were carried out by means of the SAS package (SAS Institute, Cary, NC, version 6.12) and always using all available data. Results were considered to be significant at the 5% critical level (P < 0.05).

3. Results

In our study, 8 patients were excluded because of protocol deviations, lack of data recording, or accidental removal of the catheter. A total of 41 patients with completed case report forms were included in the study (21 in the 1.5 mg/mL group and 20 in the 5 mg/mL group). For these patients, epidural catheters were functioning until the end of the observation period. Table 1 displays patients’ table and type of surgery in the 2 groups.

![Fig. 1](image)

**Fig. 1** Evolution of the mean upper sensory dermatomal level in the 2 groups of patients during the 48-hour study period. Concentration (1.5 and 5 mg/mL) refers to levobupivacaine. Error bars indicate SD. Th indicates thoracic. No significant difference between the 2 groups of patients (P = 0.68, GLMM statistic). *P < 0.05 (Student t test).
characteristics and distribution according to the type of surgery. The demographic data baseline recordings and the type of surgery were similar in the 2 groups. Specifically, there was no difference in the age range between groups.

The level of insertion of the epidural catheter was low thoracic (T9-T12), with no differences between the 2 groups ($P = 0.29$). No cases of accidental dural puncture occurred.

At the time of surgery, patients received the same amount of IV sufentanil (23 ± 9 μg in the 1.5 mg/mL group and 23 ± 7 μg in the 5 mg/mL group, $P = 0.96$). There was no difference between the groups in the amount of epidural levobupivacaine used for surgery (51 ± 16 mg in the 1.5 mg/mL group and 53 ± 14 mg in the 5 mg/mL, $P = 0.70$). Fig. 1 illustrates the mean upper level of sensory blockade at the different time points after surgery. There was no difference between the 2 groups ($P = 0.68$, GLMM statistics), except at 40 hours, whereupon there was a significantly higher mean upper level in the 1.5 mg/mL group ($P = 0.041$).

Fig. 2 shows VAS pain scores at rest and after coughing during the first 48 postoperative hours in the 2 groups. GLMM statistics of the VAS scores for pain showed no difference between the 2 groups, except that the VAS pain score was significantly superior in the 5 mg/mL group ($P = 0.045$) only at the 4-hour time point. Table 2 displays the values of the pain indicators. We noted that the scores for AUC, $V_{\text{AS}}_{\text{max}}$, $V_{\text{AS}}$ mean, and $P_{\text{VAS}} > 3$ were similar in the 2 groups. Furthermore, we highlight a strong positive relationship between the VAS scores at rest and at coughing ($r = 0.62$, $P < 0.0001$). The type of surgery did not influence the efficacy of pain relief.

Table 3 displays postoperative analgesic consumption. Mean consumption of epidural levobupivacaine during the first 24 hours amounted to 100 ± 47 mg in the 1.5 mg/mL group and 106 ± 46 mg in the 5 mg/mL group ($P = 0.35$). Propacetamol was given to all patients, and ketorolac was administered to 17 patients (81%) in the 1.5 mg/mL group and to 15 (75%) in the 5 mg/mL group ($P = 0.72$). Rescue analgesia, represented by morphine consumption (subcutaneous), was similar in the 2 groups. In the first 24 hours, the mean consumption of morphine was 7.9 ± 10.5 mg in the 1.5 mg/mL group, compared with 6.7 ± 7.0 mg for the 5 mg/mL group ($P = 0.98$). During the second postoperative day, morphine use was reduced to 1.5 ± 5.4 mg in the

### Table 2 Pain indicators, at rest and at coughing, in the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>1.5 mg/mL (n = 21)</th>
<th>5 mg/mL (n = 20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (cm$^2$)</td>
<td>56.0 ± 52.6</td>
<td>54.0 ± 28.7</td>
<td>0.59</td>
</tr>
<tr>
<td>$V_{\text{AS}}_{\text{max}}$ (cm)</td>
<td>4.3 ± 2.4</td>
<td>3.9 ± 1.9</td>
<td>0.59</td>
</tr>
<tr>
<td>$V_{\text{AS}}$ mean (cm)</td>
<td>1.2 ± 1.1</td>
<td>1.3 ± 0.8</td>
<td>0.81</td>
</tr>
<tr>
<td>$P_{\text{VAS}} &gt; 3$ (h)</td>
<td>5.9 ± 10.4</td>
<td>4.3 ± 4.8</td>
<td>0.51</td>
</tr>
<tr>
<td>At coughing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (cm$^2$)</td>
<td>89.7 ± 59.2</td>
<td>90.6 ± 49.7</td>
<td>0.96</td>
</tr>
<tr>
<td>$V_{\text{AS}}_{\text{max}}$ (cm)</td>
<td>5.6 ± 2.5</td>
<td>5.1 ± 1.9</td>
<td>0.43</td>
</tr>
<tr>
<td>$V_{\text{AS}}$ mean (cm)</td>
<td>2.1 ± 1.3</td>
<td>2.1 ± 1.1</td>
<td>0.96</td>
</tr>
<tr>
<td>$P_{\text{VAS}} &gt; 3$ (h)</td>
<td>10.4 ± 11.7</td>
<td>12.1 ± 11.0</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Concentration (mg/mL) refers to levobupivacaine.

### Table 3 Postoperative analgesic consumption in the 2 groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>1.5 mg/mL (n = 21)</th>
<th>5 mg/mL (n = 20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levobupivacaine 24 h (mg)</td>
<td>100 ± 47</td>
<td>106 ± 46</td>
<td>0.35</td>
</tr>
<tr>
<td>Levobupivacaine 48 h (mg)</td>
<td>65 ± 67</td>
<td>72 ± 68</td>
<td>0.14</td>
</tr>
<tr>
<td>Morphine 24 h (mg)</td>
<td>7.9 ± 10.5</td>
<td>6.7 ± 7.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Morphine 48 h (mg)</td>
<td>1.5 ± 5.4</td>
<td>0.4 ± 1.6</td>
<td>0.63</td>
</tr>
<tr>
<td>Propacetamol 24 h (g)</td>
<td>8 ± 0</td>
<td>8 ± 0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Propacetamol 48 h (g)</td>
<td>8 ± 0</td>
<td>8 ± 0</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>NSAIDs (n)</td>
<td>17 (81%)</td>
<td>15 (75%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Antiemetic drugs (n)</td>
<td>5 (24%)</td>
<td>7 (35%)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Concentration (mg/mL) refers to levobupivacaine. NSAIDs indicates nonsteroidal anti-inflammatory drugs.
1.5 mg/mL group versus 0.4 ± 1.6 mg in the 5 mg/mL group (P = 0.63). No life-threatening respiratory events associated with opioid administration were reported during the study period.

Finally, motor blockade was consistently low in all patients (mean Bromage score <1) without any difference between the 2 groups. Fig. 3 displays the evolution of the SBP and diastolic blood pressure. We note that arterial blood pressure (BP) was slightly lower in the 5 mg/mL group during the first 24 hours (P = 0.052, GLMM statistics), which occurred after 1, 36, and 40 hours. During the study period, no vasoconstrictors or atropine was given for treatment of hypotension or bradycardia. We point out that 5 patients (24%) in the 1.5 mg/mL group had nausea compared with 7 (35%) in the 5 mg/mL group (P = 0.43). We observed no sedation, respiratory depression, or pruritus in any patient. All patients in the 2 groups were either satisfied or very satisfied regarding the quality of their pain management.

### 4. Discussion

The results of the present study confirm that altering the concentration and the volume while maintaining equivalent total-milligram doses of levobupivacaine administered via thoracic PCEA resulted in the same quality of analgesia, both at rest and after coughing. Local anesthetic requirements were similar in both groups during the 48-hour study period. We chose to administer a 5-mg-bolus dose with a lockout interval of 20 minutes. This dose corresponds to a maximum of 15 mg/h of the local anesthetic similar to what we have used in previous studies of continuous epidural infusion [12,13]. These results are consistent with previous studies supporting the view that the quality of epidural analgesia depends on the total mass of local anesthetic and not on the volume or concentration [2,6,12-15,23].

We used plain levobupivacaine 5 mg/mL for epidural infusion at a low thoracic level. The concentration was selected to maximize the analgesic effects of the local anesthetic in the thoracoabdominal somatosensory distribution [24]. As proposed by Duggan et al [2], a low volume of a concentrated solution produces the most predictable extradural block. The cephalad extent of the sensory block (T8) was similar in both groups. We recorded only the mean upper sensory block, and therefore, we cannot make any statement about the segmental block (ie, the number of segments blocked).

We placed our epidural catheters in low thoracic vertebral interspaces, which is typical practice for patients undergoing lower abdominal surgery. However, the placement of epidural catheters in such proximity to the lumbar spinal segments, which provide motor innervation to the lower extremities, could increase the risk of motor block when compared with a midthoracic approach, especially in the high-volume group [25]. Nevertheless, lower limb motor block was consistently low in all patients, and we did not observe any difference between the 2 groups.

Although there was no statistically significant difference in hemodynamic parameters, patients in the 5 mg/mL group had a slightly lower BP without any hypotensive episodes. As previously mentioned, Liu et al [14], when using PCEA after lower abdominal surgery, observed that a lower concentration of a similar amount of epidural ropivacaine/fentanyl provides equal analgesia with less motor blockade when compared with higher concentrations of the local anesthetic. Epidural catheters were placed at the T12 to L2 interspace. Placement of catheters in proximity to lumbar spinal segments increases the risk of motor block when compared with a more cephalad approach [26]. Whiteside et al [15] using the same association of drugs after gynecologic surgery showed that a low-concentration/high-volume PCEA appears satisfactory to treat postoperative pain and reduce the dose of the drugs used in comparison with a low volume/high concentration. Our study differs considerably because we did not add any epidural opioids to focus solely on the local anesthetic action. Addition of a high volume of fentanyl to the local anesthetic could produce a more extensive sensory block as a result of greater anatomic spread and interaction with opioid receptors [9,27]. Opioids
also limit the regression of postoperative analgesia observed with local anesthetics alone and improve the quality of pain relief [28,29]. This fact makes a comparison with our results difficult.

The most important limitation related to our study design is that our patients received multimodal analgesia, which might have masked slight differences in the intensity of rest pain between the 2 groups. Nevertheless, as stated by Kehlet and Holte [30], the best quality of postoperative analgesia is achieved by systemic analgésics combined with an epidural approach. We routinely use this analgesic regimen, and we conducted our study in a clinical setting. Further studies should also examine the quality of analgesia with other infusion rate modalities (ie, supplemental night-time infusion in PCEA, as proposed by Komatsu et al [31]).

It should be noted that the plain 5 mg/mL levobupivacaine solution is ready to use. Thus, the risk of administration errors decreases, as well as the nursing time and pharmacy preparation costs.

In conclusion, the 2 concentrations of levobupivacaine (5 and 1.5 mg/mL) given as a 5-mg-bolus dose PCEA induce similar quality of postoperative analgesia without any difference in the frequency of side effects.

References


