Local anesthetics: New insights into risks and benefits
Lirk, Philipp

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Pulmonary effects of spinal anesthesia

Based on


Pulmonary effects of bupivacaine, ropivacaine, and levobupivacaine in parturients undergoing spinal anaesthesia for elective caesarean delivery: a randomised controlled study

Introduction

Intrathecal anaesthesia has replaced general as the first-line method to provide anaesthesia for elective caesarean delivery. The main reason for the popularity of spinal anaesthesia is that general anaesthesia may be associated with complications in airway management such as aspiration or failure to achieve tracheal intubation. It is unclear whether spinal anaesthesia carries a risk of significant respiratory deterioration due to motor block of respiratory muscles, since caesarean delivery necessitates a spinal block extending as far cephalad as the fourth thoracic segmental nerve. Motor blockade from the lumbar to the thoracic nerves temporarily deactivates some muscles that contribute to respiration, including the intercostal muscles and the abdominal wall muscles.

In clinical practice, bupivacaine is the most widely used local anaesthetic for elective caesarean delivery. Numerous publications have reported that spinal anaesthesia using bupivacaine significantly decreases dynamic pulmonary function parameters in the parturient. It has been suggested that the newer local anaesthetics ropivacaine and levobupivacaine do not cause the same degree of motor block, but the pulmonary effects of these drugs when used for spinal anaesthesia are unclear. For example, epidural and intrathecal levobupivacaine and ropivacaine were shown in vivo to elicit less motor block than bupivacaine. Recently, intrathecal bupivacaine was shown in parturients to have a higher potency for motor block than levobupivacaine and ropivacaine. Therefore, the pulmonary effects of ropivacaine and levobupivacaine may be less pronounced than those of bupivacaine.

The aim of the present study was to compare the performance of bupivacaine 10 mg, ropivacaine 20 mg, and levobupivacaine 10 mg for spinal anaesthesia in parturients undergoing elective caesarean delivery. As relevant endpoints, we chose to investigate dynamic maternal pulmonary function parameters and neonatal indices. Our working hypothesis was that pulmonary function would be attenuated by all three local anaesthetics.
Methods

In a single-blind study, 48 otherwise healthy parturients scheduled to undergo elective caesarean section were enrolled and randomised to receive bupivacaine, ropivacaine or levobupivacaine. Randomization of patients into the three treatment groups was performed according to a preset randomization list disclosed from sealed opaque envelopes before spinal anesthesia. Exclusion criteria were pre-existing maternal pulmonary or cardiac disease, thoracic malformation, non-singleton pregnancy, signs of fetal compromise and a body mass index (BMI) >35 kg/m², indicating severe obesity. The study was approved by the Ethics Committee of the Medical University, Innsbruck (Protocol No. UN2195_ZEK), Austria, and registered with the European Union Clinical Trials Database (EudraCT No. 2004-004649-17). Written informed consent was obtained from all patients. Patients were blinded to the study drug, but the investigator and anaesthesiologist administering spinal anaesthesia were not.

Premedication and spinal anaesthesia

All parturients were preloaded intravenously with 1000 mL of crystalloid fluid (Ringer’s lactate) and received famotidine 20 mg before transfer to the operating room. Non-invasive blood pressure, pulse oximetry and electrocardiogram were monitored. Spinal anaesthesia was performed in the sitting position between the second and fourth lumbar vertebrae using a 25-gauge Sprotte pencil-point needle (Smith, Brisbane, Australia). Patients were randomised to receive 0.5% bupivacaine 10 mg (Curasan, Kleinostheim, Germany), 1% ropivacaine 20 mg (Astra Zeneca, Södertälje, Sweden), or 0.5% levobupivacaine 10 mg (Abbott, Campoverde, Italy). Fentanyl 15 µg (Torrex Pharma, Vienna, Austria) was added to the local anaesthetic in all groups. Sensory block was tested every minute by pin prick in the mid-clavicular line, testing for discrimination between sharp and blunt stimulus, until a stable sensory block level was reached. The lowest mean arterial pressure and vasopressor requirements following spinal anaesthesia were recorded.
**Measurement of pulmonary function**

When the sensory block had stabilized, dynamic pulmonary function indices were measured using an EasyOne spirometer (ndd, Zurich, Switzerland) before spinal anaesthesia, and when a stable sensory level was achieved. The spirometer used requires several measurements tested for consistency before the best value is accepted as a result. Internal quality control software detects both implausible spirometric results and intra-test variability. Accepted results require at least two measurements of forced expiratory volume during the first second of exhalation (FEV1) or forced vital capacity (FVC) to vary no more than 200 mL. A single investigator (NK), experienced in performing spirometric measurements, recorded all pulmonary function indices; quality control and tabulation of measured data was performed blinded to group allocation. Pulmonary function tests took approximately 2 minutes to perform.

The evening before surgery, the patients were instructed in the use of the spirometer to simulate testing. Baseline measurements were obtained on the day of surgery in the 15° left lateral tilt position. To explore the possibility that the 15° left tilt and supine positions would yield different pulmonary function test results, measurements were obtained in both positions in eight patients. As there were no significant differences in pulmonary function tests, baseline results were pooled. Pulmonary function following spinal anaesthesia were measured in the 15° left tilt position. Caesarean delivery was conducted after measurements were completed.

The main outcome variables were FVC, FEV₁, and peak expiratory flow rate (PEFR). Secondary outcome variables were fetal blood gases and Apgar score. Independent factors included maternal characteristics (age, BMI, smoking status, gestational age) and perioperative data (site of puncture, time for the block to reach T4, duration of surgery, time to delivery).
Statistical analyses

Power calculation based on previous investigations of spinal anaesthesia for caesarean delivery\(^5\) assumed a mean change in FEV\(_1\) of 15-20%. Therefore, 16 test parturients per group were predicted as being necessary to detect a statistically significant alteration in function tests with a power of 85%. The primary purpose of the study was to evaluate if any of the three local anaesthetic agents cause a 15-20% decrease in FEV\(_1\) in parturients undergoing spinal anaesthesia; as such, the power analysis was not designed to indicate differences between the three agents. Normal distribution of data was checked by the Kolmogorov-Smirnov test. The time course of the main variables was tested using analysis of variance (ANOVA) with Bonferroni’s post hoc correction. Secondary variables were tested using the \(\chi^2\) test for qualitative, and ANOVA for quantitative data. \(P\) values <0.05 were considered statistically significant. The statistical null hypothesis was that pulmonary function would not be attenuated by any of the three local anaesthetics. Data were analysed using SPSS version 12.0, Chicago, IL.
Results

Demographics. The 48 parturients were between 22 and 43 years of age. There were 16 patients in each group. There were no significant differences in mean age, BMI, gestation age, smoking status or number of previous pregnancies or cesarean sections between the three groups (Table 1).

Spinal anaesthesia and surgery. The documented site of puncture varied between L2-3 (n=25) and L3-4 (n=23) but was not different between groups. The upper level of block of pin-prick sensation and the time to reach T4 did not differ between the three groups (Table 1). All caesarean deliveries were performed under spinal anaesthesia, without the need for conversion to general anaesthesia. There were no differences in duration of surgery, time to delivery after incision, lowest recorded mean arterial pressure or numbers of patients requiring vasopressors following spinal anaesthesia (Table 1).

Maternal pulmonary function tests. At baseline, the values for FVC, FEV1, and PEFR were normally distributed, and mean values for the three study groups did not differ significantly (Table 2). Forced vital capacity was decreased in the bupivacaine and ropivacaine groups but not in the levobupivacaine group. Forced expiratory volume during the first second was not decreased in any group. Peak expiratory flow rate was decreased in the ropivacaine and levobupivacaine groups. There were no significant differences in pulmonary function indices after spinal anaesthesia between the groups. To examine whether the level of spinal block would influence maternal lung function, all patients were pooled by block level, comparing the subset of patients in whom the block spread to no higher than T4 vs. higher than T4. The maternal lung function parameters after spinal anaesthesia were not different between these two groups (Table 2).

Neonatal status: there were no significant differences in neonatal outcome measures between the groups (Table 3).
Discussion

The effects of neuraxial bupivacaine on pulmonary function have repeatedly been measured, but comparative data for ropivacaine and levobupivacaine have not hitherto been available. We found a significant reduction in selected lung function parameters after intrathecal bupivacaine 10 mg, ropivacaine 20 mg and levobupivacaine 10 mg, all with fentanyl 15 µg, among patients about to undergo elective caesarean delivery. These reductions were in the region of 3-6% for FVC and 6-13% for PEFR. However, the clinical importance of this finding remains unclear. No difference was found between bupivacaine, ropivacaine and levobupivacaine in pulmonary function variables, Apgar scores or umbilical artery pH.

The propensity of ropivacaine and levobupivacaine to cause motor block is thought to be less than that of bupivacaine. One reason for this differential block may be preferential blockade of sodium channels specific for nociceptive neurones by ropivacaine. A recent investigation in parturients undergoing elective caesarean section found that intrathecal bupivacaine, levobupivacaine, and ropivacaine had high, intermediate, and low potency for motor block, respectively. In a similar study, intrathecal ropivacaine was shown to cause less intense and shorter-lasting motor block than bupivacaine. However, Camorcia et al. postulated that the differences in motor block among local anaesthetics were less distinctive when used for spinal than for epidural anesthesia.

Caesarean delivery necessitates a block to pin-prick or cold extending as far cephalad as the fourth thoracic segmental nerve. Since this blockade may affect some of the intercostal muscles, a substantial share of respiratory capability may be deactivated during spinal anaesthesia. Intercostal muscles play multifaceted roles even during physiologic inspiration and expiration. Nevertheless, Egbert et al. and Askrog et al. failed to detect clinically significant alterations in the capacity to initiate a forceful cough, presumably because of functional compensation by the diaphragm. In addition to the diaphragm, and in contrast to respiration at rest, additional muscles are required for forceful inspiration (i.e. sternocleidomastoid, scalenus, external intercostals) and expiration (i.e. internal intercostals, abdominal
Chapter 2.2

wall). Intercostal muscles after spinal blockade seem to play a minimal role in overall lung function. In our study, results for the subset of patients in whom the block extended no higher than T4 were not significantly different from those for patients in whom the block extended beyond T4. Similarly, Arai et al. recently found that maternal pulmonary function was not significantly different when comparing patients with block level of T1-T2 and T4. It remains unclear whether compensation by the diaphragm is the only factor maintaining forceful expiration in the presence of partially blocked intercostal muscles. Even patients with spinal cord injury involving the mid to lower cervical cord may be able to augment expiration using accessory muscles of respiration.

The concentrations of drugs chosen for this clinical trial were extrapolated from previous investigations, which found a relative anaesthetic potency between bupivacaine and ropivacaine of 2:1 and between bupivacaine and levobupivacaine of 1:1. Therefore, we chose final doses for bupivacaine 10 mg, levobupivacaine 10 mg, and ropivacaine 20 mg. However, in studies published after our study was initiated, different relative potencies were found. For example, Parpaglioni et al. found that the potency ratio between levobupivacaine and ropivacaine was 1:0.74, and not 1:0.5 as assumed in our study. Moreover, Camorcia et al. reported the relative ED$_{50}$ for motor block after intrathecal administration for ropivacaine:bupivacaine 0.59 and for levobupivacaine:bupivacaine 0.71, so respiratory impairment with ropivacaine might have been less than with the other two agents in our study if a more nearly equipotent dose had been used.

The addition of opioid (fentanyl 15 µg) to all local anaesthetic agents in our study could have theoretically altered the block characteristics and motor function. However, previous investigation in patients undergoing transurethral resection of the prostate demonstrated that lung function was not altered when fentanyl was added to bupivacaine for spinal anesthesia. Although fentanyl might reduce respiratory drive, it would be unlikely to affect capacity.

The dynamic pulmonary function tests were affected to different degrees by spinal anaesthesia. More specifically, FEV$_1$ did not decrease significantly in any of the study groups, which is consistent in other studies with bupivacaine. By
contrast, Kelly et al. found significant decreases in FEV\textsubscript{1} after spinal anaesthesia,\textsuperscript{3} but their results could have been confounded by an open abdomen, which has been previously shown to substantially influence pulmonary function.\textsuperscript{8}

FVC was negatively influenced by spinal anaesthesia using bupivacaine and ropivacaine, which is in accord with previous investigations.\textsuperscript{8,3} However, Harrop-Griffiths et al.\textsuperscript{2} and Arai et al.\textsuperscript{6} found no significant alterations in FVC after bupivacaine spinal anaesthesia. Possible explanations for these differences include a 12% greater BMI in our patients than among those studied by Arai and colleagues;\textsuperscript{6} the higher BMI appears to predispose patients undergoing spinal anaesthesia to more severe reductions in lung function.\textsuperscript{24 25}

Finally, PEFR decreased significantly with ropivacaine and levobupivacaine, but not with bupivacaine. While Conn et al.\textsuperscript{8} did not detect a significant deterioration of PEFR after spinal anaesthesia with bupivacaine for caesarean delivery, Harrop-Griffiths et al.\textsuperscript{2} and Kelly et al.\textsuperscript{3} reported statistically significant decreases. This disparity may be explained by different doses of bupivacaine: Harrop-Griffiths and Kelly both gave a dose of 12.5 mg. In addition, Kelly measured pulmonary function before spinal anaesthesia, and during surgery, when the abdomen was open, which may further compromise ventilation.\textsuperscript{5}

An important secondary endpoint was the analyses of Apgar scores and umbilical blood gases. In accordance with previous literature,\textsuperscript{26} no significant differences were found. To exclude the potential confounding of these results by hypotension or vasopressor administration, the lowest measured mean arterial pressure following spinal anaesthesia, and vasopressor requirements were recorded. These values were not significantly different between the groups.

Some limitations of our study should be briefly addressed. Firstly, spirometric testing depends to a large extent upon the compliance of the test person and adherence to the experimental protocol may have been difficult during the very stressful moments immediately before delivery. We sought to minimize this confounding variable by preoperative instruction, including hands-on practice with the spirometry device.\textsuperscript{2 3 8} Secondly, not all baseline measurements were taken in the same position (supine vs. 15° left tilt). Even though we performed statistical testing
to assure that these values were not different, we cannot exclude a small influence upon our results. Thirdly, our power analysis was designed to test if the groups achieved a certain decrease in pulmonary function tests, but not to evaluate differences between the groups. Because clinically significant reductions in pulmonary function were not observed in any of the groups, it seems highly unlikely that significant differences would be found between the three groups. Finally, although the present study was randomised and controlled, organisational problems precluded the use of a double-blind technique. Nevertheless, we believe that results from our study are valid and reproducible because the spirometric device required several recordings tested for consistency before computing pulmonary function indices.

The results of our study suggest that spinal anaesthesia with bupivacaine, ropivacaine, or levobupivacaine, all with fentanyl 15 µg, resulted in comparable maternal lung function (FVC, FEV₁, PEFR), and neonatal outcomes. Based on our findings, the three investigated local anaesthetics may be equally well suited for spinal anaesthesia for elective caesarean delivery.

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Table 1. Patient demographics and outcome of spinal anaesthesia

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine (n=16)</th>
<th>Ropivacaine (n=16)</th>
<th>Levobupi (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.9 ± 4.0</td>
<td>32.2 ± 5.1</td>
<td>33.9 ± 4.4</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.0 ± 3.6</td>
<td>27.5 ± 3.7</td>
<td>28.1 ± 4.9</td>
</tr>
<tr>
<td>Smokers</td>
<td>1/16</td>
<td>5/16</td>
<td>2/16</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.6 ± 1.0</td>
<td>38.4 ± 1.0</td>
<td>38.2 ± 0.8</td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Previous caesarean sections</td>
<td>1 (0-3)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Time to T4 (min)</td>
<td>6.3 ± 2.0</td>
<td>6.4 ± 1.7</td>
<td>6.7 ± 2.3</td>
</tr>
<tr>
<td>Time from incision to delivery (min)</td>
<td>9.8 ± 3.7</td>
<td>7.3 ± 3.0</td>
<td>8.7 ± 4.0</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>45.3 ± 12.5</td>
<td>46.5 ± 15.4</td>
<td>50.6 ± 12.8</td>
</tr>
<tr>
<td>Lowest mean arterial pressure (mmHg)</td>
<td>68.5 ± 10.6</td>
<td>65.7 ± 9.7</td>
<td>65.8 ± 11.4</td>
</tr>
<tr>
<td>Number requiring vasopressor</td>
<td>13</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

Values mean ± SD, median [range] or number (range). No significant differences between groups.
# Table 2. Maternal pulmonary function tests before and after spinal anaesthesia

<table>
<thead>
<tr>
<th></th>
<th>FVC (L)</th>
<th>FEV₁ (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>after</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.4*</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>3.2 ± 0.4</td>
<td>3.1 ± 0.5*</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>3.6 ± 0.5</td>
<td>3.4 ± 0.6</td>
</tr>
<tr>
<td>Block lower than T4</td>
<td>3.3 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Block higher than T4</td>
<td>3.4 ± 0.4</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>PEFR (L/s)</th>
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<tbody>
<tr>
<td></td>
<td>before</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>6.2 ± 1.2</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>5.5 ± 1.5</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>6.0 ± 1.1</td>
</tr>
<tr>
<td>Block lower than T4</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>Block higher than T4</td>
<td>3.4 ± 0.4</td>
</tr>
</tbody>
</table>

*significantly different from before: $P<0.05$ by t test, NS by ANOVA

** significantly different from before: $P<0.01$ by t test, NS by ANOVA
Table 3. Neonatal outcome

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine</th>
<th>Ropivacaine</th>
<th>Levobupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar scores 1/5/10 min</td>
<td>9/10/10</td>
<td>9/9/10</td>
<td>9/9/10</td>
</tr>
<tr>
<td>UA pH</td>
<td>7.3 ± 0.1</td>
<td>7.3 ± 0.0</td>
<td>7.3 ± 0.1</td>
</tr>
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</table>

Data are median or mean ± SD