Relative potencies of bupivacaine, levobupivacaine, and ropivacaine for neonatal spinal anaesthesia

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Background. Comparing the relative potency of new local anaesthetics such as levobupivacaine and ropivacaine with bupivacaine by the minimum local analgesic concentration model has not been described for neonatal spinal anaesthesia. This information is important to compare agents and to determine the most effective spinal dose.

Methods. We performed a two-stage study to determine the ED50, the ED95, and the relative analgesic potency of isobaric spinal bupivacaine, levobupivacaine, and ropivacaine in infants. In phase 1, 81 infants were randomized in a Dixon–Massey study to describe the minimum local analgesic dose. In phase 2, a further 70 patients were randomly allocated to receive spinal anaesthesia with doses in the upper dose–response range to define the ED 95.

Results. The ED50 doses for bupivacaine, levobupivacaine, and ropivacaine were estimated by isotonic regression to be 0.30 mg kg⁻¹ [95% confidence interval (CI) 0.25–0.43], 0.55 mg kg⁻¹ (0.50–0.64), and 0.50 mg kg⁻¹ (0.43–0.64), respectively. The ED95, respectively, of bupivacaine, levobupivacaine, and ropivacaine were 0.96 mg kg⁻¹ (95% CI 0.83–0.98), 1.18 mg kg⁻¹ (1.05–1.22), and 0.99 mg kg⁻¹ (0.73–1.50). The relative potency ratios at the ED50 were bupivacaine:levobupivacaine 0.55 (95% CI 0.39–0.88), bupivacaine:ropivacaine 0.61 (0.41–1.00), and levobupivacaine:ropivacaine 1.09 (0.84–1.45).

Conclusions. Appropriate doses for infant spinal anaesthesia are 1 mg kg⁻¹ of isobaric 0.5% bupivacaine and ropivacaine and 1.2 mg kg⁻¹ of isobaric 0.5% levobupivacaine.

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Spinal anaesthesia significantly reduces the incidence of postoperative apnoea in ex-premature infants undergoing lower abdominal surgery within the first weeks of life. Although tetracaine and bupivacaine are used at present for paediatric spinal anaesthesia, it is likely that only levobupivacaine or ropivacaine will be available in the future. These agents all demonstrate a narrow therapeutic index in infants with inadequate anaesthesia or excessively high block being common. Williams and colleagues1 used a mean dose of 0.54 mg kg⁻¹ hyperbaric tetracaine but reported a 3.8% incidence of high blocks with 0.57 mg kg⁻¹ and five infants required tracheal intubation after a dose of 0.7 mg kg⁻¹. Tetracaine has been associated with high spinal block with doses as low as 0.4 mg kg⁻¹.2 This may be due to the fact that these agents are administered at constant doses rather than based on age and size of the patient.3–5 Only rarely
have statistically rigorous methods been used to determine optimal doses\textsuperscript{6–10} or to compare different drugs\textsuperscript{11}

We have designed a two-stage adaptive dose–response study to define the minimum local anaesthetic dose (MLAD or ED\textsubscript{50}) and the ED\textsubscript{95} of bupivacaine, levobupivacaine, and ropivacaine and to compare the relative differences in potencies at these doses.

**Methods**

After institutional ethical approval and obtaining written informed consent of their parents, 151 infants of <55 weeks post-menstrual age undergoing inguinal hernia repair under spinal anaesthesia were enrolled.

Infants were fasted for 4 h before surgery. Lumbar puncture was performed in the right or left lateral decubitus position at the L4–5 interspace with a 25 G pencil-point spinal needle (Terumo Corp., Sydney, Australia) with the orifice of the spinal needle turned cephalad. Cerebrospinal fluid was aspirated and the predetermined dose of local anaesthetic injected over a 3 s interval at \( 0.25 \text{ ml kg}^{-1} \). After injection, the infants were immediately placed supine and remained at the same position for the rest of the surgery. The immediate loss of tone in the lower limbs after spinal block was taken as the initial clinical indication of an effective block for surgical anaesthesia. Sensory block was assumed to be above T10, if there was a lack of haemodynamic response to a pinch in the dermatomal distribution of the surgical incision.

Success was defined as no increase in heart rate or arterial pressure >20% above baseline values in response to surgical incision and adequate surgical anaesthesia of a duration sufficient to allow surgery. Failure was defined as inadequate motor block to permit surgery, inadequate duration of surgical anaesthesia to complete surgery, or inadequate height of block to ablate the response to surgical incision. Motor block was assessed by the clinical indication of an effective block for surgical anaesthesia, immediately after onset of motor block, at the time of initial surgical incision, and at the completion of surgery. After surgery, the infants were observed by the same observer in the post-anaesthesia recovery unit until resolution of motor block of the lower limbs. Motor block was assessed by the modified Bromage score.\textsuperscript{15}

**Statistics**

Phase 1 sample size estimation was chosen according to the recommendations of Dixon and Massey. The main outcome variable was the concentration of local anaesthetic providing adequate sensory analgesia in 50% of patients (ED\textsubscript{50} or MLAD). The SD (0.22 mg kg\textsuperscript{-1}) was based on the results of a prior study of levobupivacaine for spinal anaesthesia in ex-premature infants.\textsuperscript{6} The clinically relevant width of the 95% confidence interval (CI) for the ED\textsubscript{50} was assumed to be 0.25 mg kg\textsuperscript{-1}. A sample size of 27 per local anaesthetic was determined to be able to detect this minimum significant difference in potency with a power >90% and \( \alpha=0.05 \).

An interim analysis of the first 27 infants in each local anaesthetic group was performed to obtain an estimate of the MLAD (or ED\textsubscript{50}) from the up-down sequences using the method of Dixon and Massey.\textsuperscript{13, 14} To minimize the
bias of the starting point and any failure of stabilization, up-down estimates were also derived from the terminal six runs of patients in each group using the up-down method of Dixon and Massey.

Phase 2 of the study was designed to delineate the dose–response curve in the likely ED$_{50}$ to ED$_{95}$ range. There is no formula, which can be used to obtain the sample size required to estimate a dose quantile with a specified precision, or to estimate a ratio of dose quantiles with a given power. It was not possible to perform sample size calculations from simulations because of lack of prior knowledge of the probability of success at each dose. For these reasons, formal sample calculations were judged to be unhelpful, and the sample size was chosen for pragmatic reasons. Sample size for phase 2 was chosen to be consistent with previous studies and so as to provide additional information on the upper dose–response range. Infants were randomly allocated to doses of 0.5, 0.75, 1.00, and 1.25 mg kg$^{-1}$ for each local anaesthetic to determine the ED$_{50}$ to ED$_{95}$ range.

For each local anaesthetic, the ED$_{50}$ and ED$_{95}$ doses were estimated from the combined phase 1 and 2 data sets using the $\mu_3$ estimator after application of the pooled-adjacent violators’ algorithm, also known as isotonic regression. The 95% CIs were obtained by bootstrapping using the bias-corrected and accelerated method. Two thousand bootstrap replicates of the original data set were generated for each combination of local anaesthetic and ED$_{50}$/ED$_{95}$.

The ED$_{50}$ and ED$_{95}$ doses were also estimated after probit regression, both as a sensitivity analysis and to facilitate comparisons with previous analyses. The ED$_{50}$ and ED$_{95}$ doses were estimated as appropriate non-linear combinations of the regression coefficients using the delta method; this was implemented using the nclom command in Stata 10 (StataCorp, College Station, TX, USA).

The potency ratio of ED$_{50}$ doses obtained by isotonic regression was calculated for every pairwise combination of the three local anaesthetics (B:L, B:R, L:R); this process was repeated for the ED$_{95}$ doses. The 95% CIs for these ratios were obtained using bootstrapping, with 2000 bootstrap samples taken independently for each local anaesthetic. Associations between concentration and the duration of the spinal block for each local anaesthetic were examined using ordinary linear regression. All analyses were performed using Stata 10 statistical software.

### Results

One hundred and fifty-one infants were enrolled in the study. Outcome data were not available for three infants in the ropivacaine group due to technical difficulties with the spinal block; data for the remaining 148 infants were analysed. There were no marked differences in age, weight, type of surgery, surgery time, and duration of motor block (Table 1). No adverse events related to the local anaesthetics occurred in any infant, and there were no blocks with excessive dermatomal height.

The sequences of effective and ineffective analgesia (up-down curves) from phase 1 of the study are shown in Figure 1. ED$_{50}$ and ED$_{95}$ values obtained using three methods: the Dixon–Massey method, the isotonic $\mu_3$ estimator, and probit regression (Table 2). The Dixon–Massey method was used for interim analysis of phase 1 study data and yielded ED$_{50}$ estimates of 0.33 mg kg$^{-1}$ (95% CI 0.23–0.48) for bupivacaine, 0.48 mg kg$^{-1}$ (95% CI 0.31–0.70) for levobupivacaine, and 0.49 mg kg$^{-1}$ (0.39–0.79) for ropivacaine.

Analysis of the combined phase 1 and 2 data sets using the isotonic $\mu_3$ estimator yielded ED$_{50}$ estimates of 0.30 mg kg$^{-1}$ (0.25–0.43), 0.55 mg kg$^{-1}$ (0.43–0.64), and 0.50 mg kg$^{-1}$ (95% CI 0.43–0.64) for bupivacaine, levobupivacaine, and ropivacaine, respectively. The ED$_{95}$ estimates were 0.96 mg kg$^{-1}$ for bupivacaine (95% CI 0.83–0.98), 1.18 mg kg$^{-1}$ for levobupivacaine (95% CI 1.05–1.22), and 0.99 mg kg$^{-1}$ for ropivacaine (95% CI 0.73–1.50). The isotonic $\mu_3$ estimator produces estimates similar to those obtained with probit regression but with narrower CIs (Table 2). The exception is the ED$_{95}$ of ropivacaine where the $\mu_3$ estimate is markedly lower than the regression-based estimates. Figure 2 shows the predicted dose–response curves of the three local anaesthetics during spinal anaesthesia with the predictions obtained from probit analysis.

The potency ratios obtained from isotonic regression estimates of the ED$_{50}$ and ED$_{95}$ doses for each pairwise combination of the three doses (Table 3) show that bupivacaine is estimated to be more potent than levobupivacaine and ropivacaine at the ED$_{50}$ dose, with the ED$_{95}$ for bupivacaine being 0.55 times that of levobupivacaine (95% CI 0.39–0.88), and 0.61 times that of ropivacaine (95% CI 0.31–0.70).
Fig 1 Phase 1 (Dixon–Massey) up-down sequential allocation study of spinal bupivacaine, ropivacaine, and levobupivacaine. The testing interval was 0.125 mg kg$^{-1}$. Allocation of doses incorporated the Narayana rule which incorporates the response of the previous responses at the same dose. If there has been at least one failure in the previous two most recent responses, the dose was increased. If there are no failures in the previous two most recent responses at the current dose level, the subsequent dose was decreased. Otherwise, the dose was repeated. The calculated ED$_{50}$s are 0.3 mg kg$^{-1}$ for bupivacaine, 0.5 mg kg$^{-1}$ for ropivacaine, and 0.55 mg kg$^{-1}$ for levobupivacaine.
Bupivacaine, levobupivacaine, and ropivacaine spinal anaesthesia

Table 2 Dose–response data for bupivacaine, levobupivacaine, and ropivacaine spinal anaesthesia. Phase 1 values of ED50 with 95% fiducial limits were determined using data from the first 27 patients for each agent using the Dixon–Massey up-down sequential allocation method. Phase 2 values are doses (mg kg⁻¹) and 95% CIs. Probit and isotonic linear regression of all data from phases 1 and 2 were used to determine ED50 and ED95 values with 95% CI

<table>
<thead>
<tr>
<th>Phase</th>
<th>Bupivacaine</th>
<th>Levobupivacaine</th>
<th>Ropivacaine</th>
</tr>
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<tbody>
<tr>
<td>Phase 1</td>
<td>n=27</td>
<td>n=27</td>
<td>n=27</td>
</tr>
<tr>
<td>Dixon–Massey ED50</td>
<td>0.33 (0.23, 0.48)</td>
<td>0.47 (0.31, 0.70)</td>
<td>0.56 (0.39, 0.79)</td>
</tr>
<tr>
<td>Isotonic regression ED50</td>
<td>0.30 (0.25, 0.43)</td>
<td>0.55 (0.50, 0.64)</td>
<td>0.50 (0.43, 0.64)</td>
</tr>
<tr>
<td>ED95</td>
<td>0.96 (0.83, 0.98)</td>
<td>1.18 (1.05, 1.22)</td>
<td>0.99 (0.73, 1.50)</td>
</tr>
<tr>
<td>Probit regression ED50</td>
<td>0.27 (–0.07, 0.62)</td>
<td>0.52 (0.30, 0.73)</td>
<td>0.47 (0.21, 0.72)</td>
</tr>
<tr>
<td>ED95</td>
<td>0.96 (0.63, 1.29)</td>
<td>1.14 (0.78, 1.50)</td>
<td>1.22 (0.84, 1.60)</td>
</tr>
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</table>

Table 3 Relative potencies for bupivacaine, levobupivacaine, and ropivacaine spinal anaesthesia. ED50 and ED95 estimates were obtained from isotonic linear regression analysis. 95% CIs were bootstrapped

<table>
<thead>
<tr>
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<th>Relative potencies (95% CI)</th>
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<tr>
<td>Bupivacaine:ropivacaine ED50</td>
<td>0.61 (0.41–1.0)</td>
</tr>
<tr>
<td>ED95</td>
<td>0.97 (0.53–1.35)</td>
</tr>
<tr>
<td>Bupivacaine:levobupivacaine ED50</td>
<td>0.55 (0.39–0.88)</td>
</tr>
<tr>
<td>ED95</td>
<td>0.81 (0.59–1.10)</td>
</tr>
<tr>
<td>Levobupivacaine:ropivacaine ED50</td>
<td>1.09 (0.84–1.45)</td>
</tr>
<tr>
<td>ED95</td>
<td>1.19 (0.62–1.66)</td>
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</table>

The duration of motor block did not differ between bupivacaine, levobupivacaine, and ropivacaine in either phase 1 or phase 2 (Table 4). At concentrations greater than the ED95, duration of motor block was 81.9 (SD 17.6) min for bupivacaine (n=12), 87.5 (SD 9.9) min for levobupivacaine (n=4), and 85.2 min (SD 30.6) for ropivacaine (n=21). There is very strong evidence for an association between dose and duration for all agents (P<0.001 for bupivacaine and ropivacaine, P=0.004 for levobupivacaine). Each increase in concentration of 0.10 mg kg⁻¹ is estimated to increase the spinal duration by 5.6 min for bupivacaine (95% CI 3.4–7.8 min), 3.7 min (95% CI 1.3–6.1 min) for levobupivacaine, and 4.1 min (95% CI 2.4–5.7 min) for ropivacaine.

Discussion

The ED50 for spinal anaesthesia in infants with isobaric spinal bupivacaine, ropivacaine, and levobupivacaine are 0.3, 0.55, and 0.50 mg kg⁻¹ respectively. The ED95 values for isobaric spinal bupivacaine, ropivacaine, and levobupivacaine are 0.96, 1.18, and 0.99 mg kg⁻¹, respectively. Bupivacaine is estimated to be more potent than either ropivacaine or levobupivacaine at the ED50 and ED95 doses. The potency difference is less marked at the ED95 dose. Levobupivacaine and ropivacaine had similar potency ratios at both ED50 and ED95.
Most previous minimum local anaesthetic concentration (MLAC) or MLAD studies have been performed in adults. However, some studies have suggested that ropivacaine is 40% less potent than bupivacaine, with 9% less ropivacaine required at the ED50 but 7% less levobupivacaine required at the ED95; these effect sizes are small. A potency order of bupivacaine, levobupivacaine, and ropivacaine has been determined in obstetric epidural and spinal studies. Bupivacaine is consistently more potent than the other local anaesthetics, but the relative difference in the potencies of ropivacaine and levobupivacaine is inconsistent with ratios varying from 0.6 to 1. The reported ropivacaine:levobupivacaine ratio of 0.76 was noted to increase to 0.82 when adjusted for molar potency. Reported potency ratios are R:B 0.59, R:L 0.83, and L:B 0.71. Studies in obstetric patients based on up-down sequential allocation designs have suggested that ropivacaine is 40% less potent than bupivacaine. The relative potency ratios for motor block after intrathecal anaesthesia for Caesarean section were ropivacaine:bupivacaine 0.59, ropivacaine:levobupivacaine 0.83, and levobupivacaine:bupivacaine 0.71. However, some studies have suggested that ropivacaine and levobupivacaine are equipotent.

Our dose–response curves agree with those reported by van de Velde and colleagues, in which levobupivacaine and ropivacaine have ED50 values which are similar to each other but markedly different from bupivacaine. At clinically relevant doses, however, the dose–response curves of bupivacaine, ropivacaine, and levobupivacaine begin to converge. Studies reporting differences in the ED50 of local anaesthetics assume the dose–response curves to be parallel and therefore generalize the differences in potency to the entire dose–response curve. This assumption has been challenged with suggestions that the potency ratio is not fixed but dose-dependent. This has been demonstrated with the potency ratio of bupivacaine relative to lidocaine, in which the relative potency of bupivacaine increases as the concentration or dose is reduced.

The dose–response curve for bupivacaine spinal anaesthesia in neonates and infants has not previously been described. Previous studies have used isobaric bupivacaine (mean dose 0.8 mg kg\(^{-1}\)), bupivacaine 0.5% (0.3–1 mg kg\(^{-1}\)), or bupivacaine 0.75% in dextrose 8.25% (0.6–1 mg kg\(^{-1}\)) in infants, more than 6 months of age, tetracaine (0.2–0.4 mg kg\(^{-1}\)) and bupivacaine (0.2–0.6 mg kg\(^{-1}\)) are recommended. From our bupivacaine dose–response data, these doses are in the ED50 to ED95 range. Comparison with these reports is difficult because sensory levels of anaesthesia and analgesia are not recorded, and there is no consensus on the optimal sensory block level to be reached for lower abdominal surgery in neonates.

In our study, ropivacaine and levobupivacaine were 39–45% less potent than bupivacaine at ED50 values but 19–21% less potent at ED95 values. No clear picture emerges as to the relative potency of spinal levobupivacaine and ropivacaine, with 9% less ropivacaine required at the ED50 but 7% less levobupivacaine required at the ED95; these effect sizes are small. A potency order of bupivacaine, levobupivacaine, and ropivacaine has been determined in obstetric epidural and spinal studies. Bupivacaine is consistently more potent than the other local anaesthetics, but the relative difference in the potencies of ropivacaine and levobupivacaine is inconsistent with ratios varying from 0.6 to 1. The reported ropivacaine:levobupivacaine ratio of 0.76 was noted to increase to 0.82 when adjusted for molar potency. Reported potency ratios are R:B 0.59, R:L 0.83, and L:B 0.71. Studies in obstetric patients based on up-down sequential allocation designs have suggested that ropivacaine is 40% less potent than bupivacaine. The relative potency ratios for motor block after intrathecal anaesthesia for Caesarean section were ropivacaine:bupivacaine 0.59, ropivacaine:levobupivacaine 0.83, and levobupivacaine:bupivacaine 0.71. However, some studies have suggested that ropivacaine and levobupivacaine are equipotent.

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Table 4 Duration of motor block. Phase 1 is the Dixon–Massey up-down sequential allocation phase. Phase 2 is the dose-escalation phase. Motor block was assessed by a modified Bromage score.

<table>
<thead>
<tr>
<th>Doses</th>
<th>Phase 1–2</th>
<th>Mean (n)</th>
<th>95% CI (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>n</strong></td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>51</td>
<td>70.2 (22.7)</td>
<td>63.8, 76.6</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>50</td>
<td>81.7 (20.7)</td>
<td>75.8, 87.6</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>47</td>
<td>66.0 (25.4)</td>
<td>58.6, 73.5</td>
</tr>
<tr>
<td></td>
<td><strong>ED50 (Phase 1+2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>12</td>
<td>81.9 (21.5)</td>
<td>68.2, 95.6</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>4</td>
<td>87.5 (10.0)</td>
<td>71.6, 103.4</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>21</td>
<td>85.2 (19.2)</td>
<td>76.5, 94.0</td>
</tr>
</tbody>
</table>

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such should be equally potent. The greater lipid solubility of bupivacaine becomes more apparent in the intrathecal space near the spinal cord and this means greater partition into the spinal cord and almost inevitable motor blocking effects. The differences in the potency between levobupivacaine and bupivacaine spinal anaesthesia in infants may be attributed to differences in pharmacodynamic rather than pharmacokinetic responses.

In our series, duration of motor block at concentrations greater than the ED$_{95}$ was 81.9 min for bupivacaine, 87.5 for levobupivacaine, and 85.2 for ropivacaine. These values call into question the proposed advantages of additives such as glucose, clonidine, or epinephrine to improve duration of neonatal spinal anaesthesia.28 30 31 37

The value of up-down studies has been challenged as they concentrate doses solely around the midpoint of the dose–response curve.38 39 Instead of determining the ED$_{50}$ and extrapolating it to an ED$_{95}$, we attempted to populate the upper dose–response range. Advantages of this include a large sample size relative to other studies and the fact that patients were randomized to agents, helping to ensure that the patients assigned to each agent did not differ systematically. A disadvantage of the study design is that in attempting to estimate both ED$_{50}$ and ED$_{95}$ for each agent with a two-stage design, rather than targeting a single quantile, some precision may have been sacrificed at either quantile. In particular, 95% CIs for isotonic estimates that include the highest or lowest dose given for an agent need to be interpreted with caution; the true confidence limit is likely to be higher or lower, respectively, but cannot be properly estimated using the isotonic $\mu_3$ estimator, which constrains estimates to lie within the range of doses actually given. This problem would have been alleviated in a study which targeted a single quantile using a biased coin design.16

Bupivacaine is estimated to be more potent than either ropivacaine or levobupivacaine at the ED$_{50}$ dose. The potency difference, however, is less marked at the ED$_{95}$ dose. Levobupivacaine and ropivacaine were of similar potency at both ED$_{50}$ and ED$_{95}$. An appropriate dose for infant spinal anaesthesia is 1 mg kg$^{-1}$ of isobaric 0.5% bupivacaine and ropivacaine and 1.2 mg kg$^{-1}$ of isobaric 0.5% levobupivacaine. At these doses, duration of surgical anaesthesia should last $\sim$80 min. Although no adverse events or excessively high blocks were encountered in this study, caution is warranted in exceeding these doses.

Supplementary material

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