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

\[ \text{maximum total dose of } 2.5 \text{ mg kg}^{-1} \]

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 saphenous cord or peritoneal traction during inguinal hernia repair.

If the spinal was inadequate for surgery, rescue was provided with general anaesthesia using sevoflurane and the surgical site was infiltrated with bupivacaine to a maximum total dose of 2.5 mg kg\textsuperscript{-1}.

Phase 1 was an up-down sequential allocation study. Infants were randomized to one of the three groups, by using a computer-generated list, to receive spinal anaesthesia with one of the three local anaesthetics: bupivacaine 0.5% (Pfizer, Sydney, Australia), levobupivacaine (Abbott Australasia, Sydney, Australia), or ropivacaine (AstraZeneca, Sydney, Australia). The first infant received 0.25 ml kg\textsuperscript{-1} (1.25 mg kg\textsuperscript{-1}) of 0.5% local anaesthetic. In subsequent patients, the dose of local anaesthetic received was determined by the success or failure of surgical anaesthesia achieved by the previous patients, according to Dixon’s up-down sequential allocation method.\textsuperscript{12,13} The Narayana rule\textsuperscript{14} was introduced to improve the precision of estimation of the ED\textsubscript{50} by incorporating 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 were no failures in the previous two most recent responses on the current dose level, the subsequent dose was decreased. Otherwise, the dose was repeated. The dose interval was set at 0.025 ml kg\textsuperscript{-1} of 0.5% local anaesthetic (0.125 mg kg\textsuperscript{-1}).

A conservative threshold upper limit of 1.5 mg kg\textsuperscript{-1} (0.3 ml kg\textsuperscript{-1}) was set to minimize the risk of excessive height of sensory block. The minimum dose was not defined consistent with the up-down method. To facilitate dose–response analysis, outcomes were recorded as a dichotomous outcome (effective or ineffective). To calculate the MLAD with sequential allocation (up-and-down technique), we predetermined a minimum number of independent negative–positive up-and-down deflections of >6. The stopping rule required the recruitment of more than 20 infants.

Phase 2 was a dose-escalation study. After interim analysis of the phase 1 results, four dose levels above the calculated ED\textsubscript{50} were defined. Dose spacing was set at 0.05 ml kg\textsuperscript{-1} of 0.5% local anaesthetic (0.25 mg kg\textsuperscript{-1}) consistent with the re-estimated standard deviation (SD). Defined levels were set at 0.5, 0.75, 1.0, and 1.25 mg kg\textsuperscript{-1} of 0.5% local anaesthetic. Criteria for success, failure, excessive height of sensory block, and duration of motor block were identical to those in phase 1. Infants were randomly allocated to local anaesthetic and dose with the help of a computer-generated list. An independent observer, blinded to spinal dose, recorded non-invasive arterial pressure, heart rate, and haemoglobin oxygen saturation before the initiation of spinal 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 nlcom 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

Table 1

<table>
<thead>
<tr>
<th>Local Anaesthetic</th>
<th>$ED_{50}$ (mg kg$^{-1}$)</th>
<th>$ED_{95}$ (mg kg$^{-1}$)</th>
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<tbody>
<tr>
<td>Bupivacaine</td>
<td>0.33 (0.23–0.48)</td>
<td>0.96 (0.83–0.98)</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.48 (0.31–0.70)</td>
<td>1.18 (1.05–1.22)</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.49 (0.39–0.79)</td>
<td>0.99 (0.73–1.50)</td>
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Table 2

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>$ED_{50}$ (mg kg$^{-1}$)</th>
<th>$ED_{95}$ (mg kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-menstrual age (weeks)</td>
<td>7.4 (3.4)</td>
<td>6.9 (3.9)</td>
</tr>
<tr>
<td>Current age (weeks)</td>
<td>3.8 (0.9)</td>
<td>3.6 (0.8)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>27.1 (7.6)</td>
<td>31.6 (13.7)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>$ED_{50}$ (mg kg$^{-1}$)</td>
<td>$ED_{95}$ (mg kg$^{-1}$)</td>
</tr>
<tr>
<td>Post-menstrual age (weeks)</td>
<td>42.3 (2.9)</td>
<td>44.4 (4.1)</td>
</tr>
<tr>
<td>Current age (weeks)</td>
<td>7.8 (3.6)</td>
<td>8.9 (3.5)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>29.4 (7.8)</td>
<td>33.0 (10.7)</td>
</tr>
</tbody>
</table>
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 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.

Discussion

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.
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.22 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$^{-1}$),27 bupivacaine 0.5% (0.3–1 mg kg$^{-1}$),28–29 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 ED$_{50}$ to ED$_{85}$ 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 ED$_{50}$ values but 19–21% less potent at ED$_{75}$ values. No clear picture emerges as to the relative potency of spinal levobupivacaine and ropivacaine, with 9% less ropivacaine required at the ED$_{50}$ but 7% less levobupivacaine required at the ED$_{75}$; 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 1.24 25 32 The reported ropivacaine:levobupivacaine ratio of 0.76 was noted to increase to 0.82 when adjusted for molar potency.25 Reported potency ratios are R:B 0.59, R:L 0.83, and L:B 0.71;21 L:B 0.87, R:B 0.76, and R:L 0.88,32 and R:L 0.69.25 Our findings agree with those of Van de Velde and colleagues24 who reported that bupivacaine is 1.5 times more potent than either levobupivacaine or ropivacaine whereas levobupivacaine and ropivacaine are of equal potency (ratio 1) but differ from those of Parpaglioli and colleagues23 who reported a potency ratio of spinal R:L of 0.75.

Differences in potency between the three local anaesthetics are to be expected because of differences in formulation, lipid solubility, and intrinsic vasoconstrictor activity. Because of its formulation, levobupivacaine contains 12.6% more active molecules than bupivacaine and 11% less than ropivacaine. Levobupivacaine has 7.5% more active molecules than ropivacaine because levobupivacaine is formulated as the base not the hydrochloride salt and ropivacaine’s molecular weight is less than levobupivacaine (274 vs 288). Therefore, based on molar weights, the potency order should be bupivacaine, levobupivacaine, and then ropivacaine. Lipid solubility is primarily responsible for local anaesthetic potency. With an n-octanol:water partition coefficient of 115, ropivacaine is less lipid soluble than bupivacaine (346) and therefore should be less potent. Levobupivacaine and bupivacaine have the same octanol:water solubility coefficient and as

Most previous minimum local anaesthetic concentration (MLAC) or MLAD studies have been performed in adults.20–22 Studies in pregnancy have estimated the relative potencies of bupivacaine, levobupivacaine, and ropivacaine from MLAC and MLAD studies, but potency ratios are not uniform and at times are contradictory.20–23 This may be partly due to variation in parity, dystocia, stage of labour, and starting visual analogue pain scores, all of which have a significant impact on calculated MLAC and MLAD values. Spinal anaesthesia in infants provides an ideal model for comparing local anaesthetic potencies because of the relatively homogenous population, the clearly defined endpoint of motor block, and the absence of other pharmacological (opioids and clonidine) or physiological (pregnancy) confounding factors.

Only six adult studies21–25 and two paediatric studies5 7 have attempted to describe dose–response curves for spinal ropivacaine or levobupivacaine. There have been no data comparing the relative analgesic potencies of spinal bupivacaine, ropivacaine, and levobupivacaine in children. Adult studies comparing the minimum local analgesic doses of intrathecal levobupivacaine and ropivacaine have reported conflicting results.21–26 Studies in obstetric patients based on up-down sequential allocation designs have suggested that ropivacaine is 40% less potent than bupivacaine.20–23 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 0.71.20 However, some studies have suggested that ropivacaine and levobupivacaine are equipotent.24

Our dose–response curves agree with those reported by van de Velde and colleagues,24 in which levobupivacaine and ropivacaine have ED$_{50}$ 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 ED$_{50}$ of local anaesthetics assume the dose–response curves to be parallel and therefore generalize the differences in potency to the entire dose–response curve.22 This assumption has been challenged with suggestions that the potency ratio is not fixed but dose-dependent. This has

<table>
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<tr>
<th>Phase 1</th>
<th>Mean (SD)</th>
<th>95% CI (min)</th>
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<tbody>
<tr>
<td>Bupivacaine</td>
<td>70.2 (22.7)</td>
<td>63.8, 76.6</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>81.7 (20.7)</td>
<td>75.8, 87.6</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>66.0 (25.4)</td>
<td>58.6, 73.5</td>
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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.
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.33–36

In our series, duration of motor block at concentrations greater than the ED$_{50}$ 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 estimators 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, than that in attempting both quantiles. In particular, 95% CIs for isotonic estimators that constrain estimates to lie within the dose–response curve. Instead of determining the ED$_{50}$ and ED$_{95}$ it is possible to use 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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