Anesthesiology 2010; 113:445–53

Determination and Comparison of Graded Dose–Response Curves for Epidural Bupivacaine and Ropivacaine for Analgesia in Laboring Nulliparous Women

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ABSTRACT

Background: The potencies of bupivacaine and ropivacaine have been compared using up-and-down methodology, but their complete dose–response curves have not been compared. The authors performed a random allocation-graded dose–response study of epidural bupivacaine and ropivacaine given epidurally for labor analgesia.

Methods: Three hundred laboring nulliparous patients were randomly given epidural bupivacaine (5, 10, 15, 20, 30, or 40 mg) or ropivacaine (7, 15, 20, 30, 45, or 60 mg) in 20 ml of saline. Visual Analog Scale pain scores were recorded for 30 min. Response was defined by the percentage decrease in pain score from baseline at 30 min, and dose–response data were analyzed by using nonlinear regression.

Results: Sigmoidal E_{max} model dose–response curves were fitted to the datasets for bupivacaine ($R^2 = 0.53$) and ropivacaine ($R^2 = 0.59$). The curves had similar steepness (Hill coefficient 2.02 [95% CI, 1.55–2.50] *vs.* 2.25 [1.70–2.79], $P = 0.55$). The ED_{50} (dose of the drug that reduces pain score to 50% of baseline at 30 min, also known as D_{50}) of ropivacaine was greater than that of bupivacaine (15.3 [95% CI 13.7–17.1] mg *vs.* 11.3 [10.0–12.7] mg, $P = 0.0003$), but ED_{90} (D_{90}) was similar (40.6 [32.4–51.1] mg *vs.* 33.4 [26.2–42.7] mg, $P = 0.29$). The potency ratio at ED_{50} for ropivacaine:bupivacaine was 0.75 (95% CI, 0.65–0.88).

Conclusions: Ropivacaine is less potent than bupivacaine, but otherwise they have similar dose–response characteristics. The difference in potency is not statistically significant at ED_{90} doses.

What We Already Know about This Topic

- The dose of epidural ropivacaine is greater than bupivacaine to achieve adequate labor analgesia in 50% of women, but there is little full dose-response data

What This Article Tells Us That Is New

- Using randomized dosing in 300 parturients, ropivacaine was 25% less potent than bupivacaine to achieve analgesia in 50% of women
- At a more clinically relevant dose to achieve analgesia in 90% of women, bupivacaine and ropivacaine were equipotent

SEVERAL recent studies have compared the potencies of bupivacaine and ropivacaine when given epidurally for labor analgesia.[1,2] Almost exclusively, these studies have used up-and-down methodology (UDM) and have been designed to determine and compare values for the EC_{50}—the concentration that produces an effective response (however defined) in 50% of the population, which has also been referred to as the minimum local anesthetic concentration.[3] Using this methodology, the potency ratio of ropivacaine:bupivacaine has been estimated to be 0.6.[1,2] Similar estimates of comparative potency have been made for other local anesthetic pairs.[3,4] However, UDM has a number of important limitations. For example, EC_{50} values are not of as much interest to clinicians as values at higher points (quantiles) on the dose–response curve such as EC_{90} or EC_{95}; furthermore, UDM studies provide no information on the shapes of the dose–response curves, and differences in relative potency at higher quantiles may not be the same as at the EC_{50}. Furthermore, UDM studies and random

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Received from Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China. Submitted for publication August 25, 2008. Accepted for publication April 6, 2009. Supported by a Direct Grant for Research from the Chinese University of Hong Kong, Shatin, Hong Kong, China (grant no. 2040834) and by departmental funds. Presented in part as a poster at the International Anesthesia Research Society 79th Clinical and Scientific Congress, Honolulu, Hawaii, March 14th, 2005.

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allocation dose–response studies that use methods such as probit and logit analyses are based on binary or quantal outcomes that do not fully use data such as pain scores, which are frequently measured on continuous scales.

In this study, we have performed a graded dose–response study of bupivacaine and ropivacaine given epidurally to nulliparous women for analgesia in the first stage of labor. Rather than a sequential UDM design, we used the more traditional technique of blinded random allocation to a range of doses of each local anesthetic and rather than using a binary outcome, the response to each local anesthetic dose was quantified in terms of the proportional decrement in Visual Analog Scale (VAS) pain score. Data were analyzed using nonlinear regression. Our objectives were to characterize the complete dose–response curves of epidural bupivacaine and ropivacaine to compare the slopes of the curves and to compare estimates of potency.

Materials and Methods

Approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong, Shatin, Hong Kong, China. We recruited a total of 300 patients requesting epidural pain relief in labor into this randomized, double-blinded trial. Inclusion criteria were American Society of Anesthesiologists physical status 1 or 2, nulliparous, uncomplicated singleton pregnancy, ≥ 36 weeks' gestation, cephalic presentation, established labor with cervical dilatation ≤ 5 cm, baseline VAS pain score ≥ 50 mm (scale: 0–100 mm). Exclusion criteria were inability or unwillingness to give informed consent, parenteral opioid received within the preceding 2 h, any contraindication to epidural analgesia or allergy to local anesthetics. Written informed consent was obtained for all patients in a two-stage procedure. Initially, suitable patients were approached by a research nurse soon after admission to the labor ward, written and verbal information about the study was given, and preliminary consent to participate was obtained. Subsequently, if a patient requested epidural analgesia, compliance with inclusion and exclusion criteria was checked, consent was confirmed, and the patient was entered into the study. Patients were only recruited during office hours when members of the investigating team were available.

The study was conducted in two phases. First, according to the initial study design, 250 patients were recruited and randomized, by drawing of shuffled, opaque, coded envelopes, to one of the 10 groups ($n = 25$ per group) to receive an epidural bolus of bupivacaine (10, 15, 20, 30, or 40 mg) or ropivacaine (15, 20, 30, 45, or 60 mg) on request for epidural analgesia. The two drugs were studied concurrently so that an enrolled patient would receive a randomized dose of either bupivacaine or ropivacaine. The doses were chosen assuming an anticipated ropivacaine:bupivacaine potency ratio of 0.6[1,2] and were spaced so that the logarithms of the doses for each drug would be approximately evenly spaced. Doses were rounded to convenient numbers for ease of preparation. After patient recruitment in the first phase was complete, preliminary analysis of the data showed that the dose–response curves for both drugs were incompletely defined in the lower dose range.[5] Therefore, a second phase of the study was planned with approval from the local ethics committee. A further group of patients was recruited and randomized to receive either 5 mg of bupivacaine or 7 mg of ropivacaine (n = 25 per group). The consent process for the second phase of the study included specific information that small doses of local anesthetic were being investigated. All procedures and all aspects of clinical management were identical to the first stage of the study. The second phase of the study was registered in the Centre for Clinical Trials Clinical Registry of the Chinese University of Hong Kong (unique trial no. CUHK_CCT00126).

All study doses were prepared in identical syringes by an investigator not involved in patient assessment and were diluted to a volume of 20 ml with isotonic sodium chloride solution. Patients were instructed in the use of a 100-mm VAS pain ruler, and baseline measurements of pain, blood pressure, and heart rate were made. Intravenous prehydration of 500 ml of lactated Ringer's solution was given. With aseptic precautions, after local skin infiltration with lidocaine, the epidural space was located with an 18- or 16-gauge Tuohy needle at what was estimated to be the L2–3 or L3–4 interspace, using the technique chosen by the attending anesthesiologist. A multiorifice catheter was inserted 4 cm into the epidural space, and the patient was turned supine with left lateral uterine displacement. After aspirating the epidural catheter and checking for the presence of blood or cerebrospinal fluid, the study dose of local anesthetic was then injected epidurally. Initially, 5 ml of solution was injected. Five minutes later, after observing for any signs of intravenous or intrathecal injection, the remaining 15 ml was injected. "Time zero" was defined as the time of completion of injection of the first 5 ml.

After epidural injection, further VAS pain scores at the peak of a uterine contraction were measured at the nearest 5-min interval until 30 min. At the same time, we monitored maternal blood pressure and heart rate in addition to continuous cardiotocography, and we assessed sensory level with ice and motor block by using the modified Bromage scale (0 = no motor block; 1 = inability to raise the extended leg, able to move knees and feet; 2 = inability to raise the extended leg and to move knees, able to move feet; and 3 = complete motor block of the lower limbs). The primary outcome used for analysis was the decrease in VAS pain score at 30 min compared with baseline. If analgesia was not considered adequate by the patient at 30 min, a "rescue" bolus of 5 ml of bupivacaine (0.25%) was given and repeated up to two times at 15-min intervals as required. If analgesia was still inadequate 15 min after a third rescue bolus, the epidural catheter was declared nonfunctional and was resited, and the patient was withdrawn from the study. For such cases, the next patient recruited was allocated to the same study dose as a replacement. The study was terminated after 30 min when adequate analgesia was obtained and subsequent management was at the discretion of the attending team according to usual practice. Hypotension was defined as a decrease in systolic blood pressure to less than 20%, less than baseline,

and less than 100 mmHg, and it was treated with intravenous fluid and vasopressors according to usual practice. Obstetric management was according to normal labor ward protocols.

Statistical Analysis

Sample size was determined empirically based on data from our previous dose–response study of epidural ropivacaine in labor.[6] In that study, 15 patients were allocated to each dose, and estimates of the ED_{50} and ED_{95} were determined but with wide CIs (73–138% and 63–158% of the estimated values, respectively). Therefore, in this study, to achieve more narrow CIs, we arbitrarily decided to increase the number of patients allocated to each dose group to 25.

Univariate comparisons among dose groups for each drug were made using ANOVA or the Kruskal–Wallis test as appropriate using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL). Dose–response analysis was performed using GraphPad Prism 5.01 (GraphPad Software, Inc., La Jolla, CA). Data were initially entered into Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA) and subsequently imported into GraphPad Prism. Values for dose were entered as x values and were log transformed. Response data were entered as y values after normalization of pain scores according to the following formula:

$$response = \frac{initial\ VAS\ pain\ score - VAS\ pain\ score\ at\ 30\ min}{initial\ VAS\ pain\ score} \times 100\% \quad (1)$$

A variable slope E_{max} model sigmoidal (four-parameter logistic) dose–response curve was fitted to the data for each local anesthetic, with the bottom parameter (minimum response) constrained to equal zero and the top parameter (maximum response) constrained to equal 100, using the following equation:

$$Y = \frac{100 \times \text{dose}^{\gamma}}{\text{dose}^{\gamma} + ED_{50}{}^{\gamma}} \quad (2)$$

(where Y is the response as a percentage and γ is the Hill coefficient or Hillslope).

GraphPad Prism uses an iterative approach to generate best-fit curves for the data. Parameters are adjusted to minimize the sum of squares (the sum of the squares of the vertical distances of data points from the curve) using the algorithm of Marquardt.[7] Values for $\log(ED_{50})$, ED_{50}, and Hill coefficient (Hillslope) were calculated with 95% CIs.

To obtain values for ED_{90}, equation (2) was first rearranged:

$$dose = \left(\frac{Y}{100-Y}\right)^{1/\gamma} \times ED_{50} \quad (3)$$

Then, substitution into equation (3) was performed for $Y = 90\%$:

$$ED_{90} = \left(\frac{90}{100-90}\right)^{1/\gamma} \times ED_{50} \quad (4)$$

This equation was entered into GraphPad Prism and values for $\log(ED_{90})$ and ED_{90} with 95% CIs were generated.

To compare the dose–response curves of bupivacaine and ropivacaine and to determine their relative potency, GraphPad Prism was set to compare two models. In the first model (null hypothesis), the data were fitted with the assumption that the datasets for the two local anesthetics shared the same best-fit value of $\log(ED_{50})$. In the second model (alternative hypothesis), the data were fitted with the assumption that the best-fit values of $\log(ED_{50})$ were distinct. The models were then compared with the extra sum-of-squares F test.[8] The procedure was repeated to compare values of Hill coefficient and ED_{90}. The relative potency ratio of ropivacaine: bupivacaine at ED_{50} with 95% CIs was calculated using the EC_{50} Shift equation of GraphPad Prism. Values of $P < 0.05$ were considered significant for all comparisons.

In addition to the above analyses, a secondary analysis was performed, which used a quantal (dichotomous) outcome. The purpose of this secondary analysis was to provide comparison with previously published studies that have used this type of analysis. For this, a positive response ("success") was defined, according to convention for studies of drug potency, as a half-maximal effect. In our data, this equated to a decrease in VAS pain score to ≤ 50 of the baseline value at 30 min, which is the same endpoint as used in our previous dose–response study of epidural ropivacaine.[6] For each drug, the numbers of responders at each dose level were tallied, and probit regression was used to calculate values for ED_{50} and ED_{90} with 95% CIs and an estimate of relative median potency was determined by comparing the values of ED_{50}. This secondary analysis was performed using SPSS 15.0 for Windows.

Results

Data collection was completed within 34 months for the first stage of the study and within 8 months for the second stage. Recruitment of patients is summarized in figure 1. Overall, preliminary consent was obtained from a total of 805 patients of whom 334 patients were recruited with data analyzed for 300 patients. Patient characteristics were similar among dose groups for each local anesthetic (table 1). Baseline pain scores, time from injection of the study dose to the first epidural topup, sensory and motor changes, and the incidence of hypotension are summarized in table 2. There were significant trends toward a higher maximum level of sensory block ($P < 0.001$) and a longer duration of initial analgesia ($P < 0.001$) with increasing dose for both local anesthetics. In addition, there was a trend toward a greater incidence of hypotension with increasing dose that was significant for ropivacaine ($P = 0.001$) but not for bupivacaine ($P = 0.04$). The incidence of motor block was small and similar among groups.

The dose–response curves that were fitted to the data for both local anesthetics are shown in figure 2. Derived parameters for the curves are shown in table 3. The calculated values for ED_{50} with 95% CIs for bupivacaine and ropivacaine were 11.3 (10.0–12.7) and 15.3 (13.7–17.1) mg, respectively, and the calculated values for ED_{90} with 95% CIs were 33.4 (26.2–42.7) and 40.6 (32.4–51.1) mg, respectively.

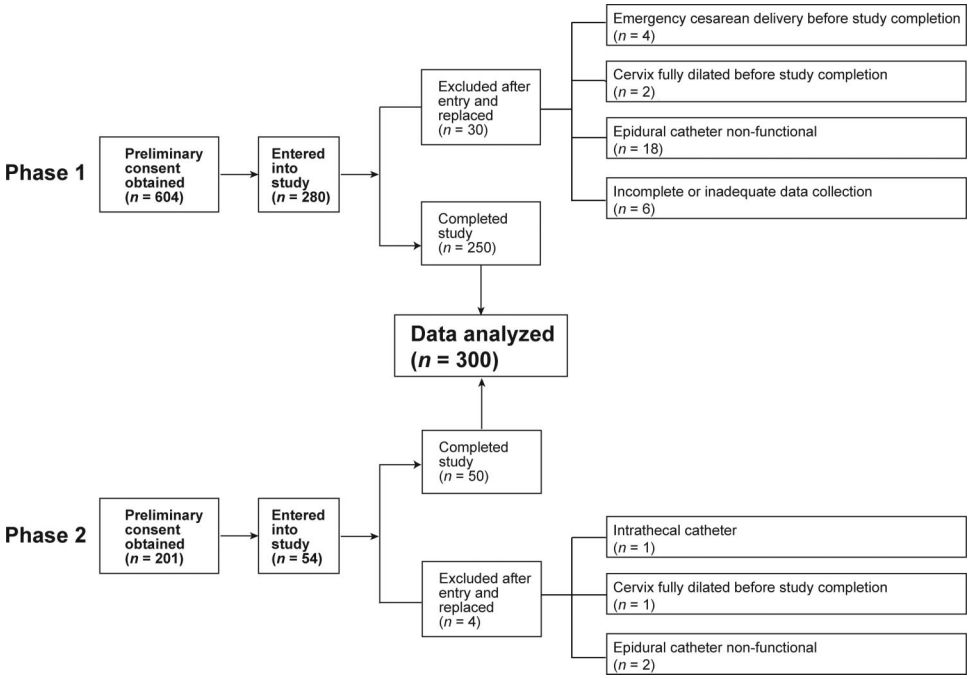

Fig. 1. Flow diagram showing recruitment of patients. Phase 2 of the study was commenced after completion of phase 1.

The equations for the curves that were fitted to each local anesthetic were as follows:

Bupivacaine:

$$Y = \frac{100 \times \text{dose}^{2.02}}{\text{dose}^{2.02} + 134} \quad (5)$$

Ropivacaine:

$$Y = \frac{100 \times \text{dose}^{2.25}}{\text{dose}^{2.25} + 463} \quad (6)$$

Comparison of the two datasets showed that ED_{50} was significantly different between bupivacaine and ropivacaine ($P = 0.0003$) but the Hill coefficient ($P = 0.55$) and ED_{90} ($P = 0.29$) were similar. The potency ratio for ropivacaine: bupivacaine obtained by comparing values for ED_{50} was 0.75 (95% CI 0.65–0.88).

Results of the secondary analysis performed using probit regression showed that the calculated values for ED_{50} with 95% CIs for bupivacaine and ropivacaine were 11.6 (7.8–15.8) and 16.4 (11.1–22.4) mg, respectively, and the calculated values for ED_{90} with 95% CIs were 24.9 (18.1–41.5) and 35.0 (25.3–59.7) mg, respectively. The median potency ratio for ropivacaine:bupivacaine obtained from this analysis was 0.71 (95% CI 0.36–1.11).

Discussion

In this study, we have determined dose–response curves for bupivacaine and ropivacaine given epidurally to nulliparous pa-

Table 1. Patient Characteristics

	Dose						
	5 mg	10 mg	15 mg	20 mg	30 mg	40 mg	*P* Value
Bupivacaine							
Age, yr	29.2 (5.6)	27.2 (4.7)	28.2 (4.8)	28.3 (4.3)	30.7 (5.4)	28.6 (4.9)	0.23
Weight, kg	68.4 (9.6)	65.7 (6.7)	65.2 (9.5)	66.4 (8.9)	67.7 (9.9)	69.5 (7.2)	0.48
Height, cm	159 (5)	156 (5)	157 (4)	159 (7)	158 (5)	158 (5)	0.29
Cervical dilatation, cm	2 (1–3)	1 (1–2)	2 (1–2)	2 (2–3)	2 (1–2)	2 (1–2.5)	0.08
Oxytocin use (n)	15 (60%)	15 (60%)	14 (56%)	15 (60%)	14 (56%)	16 (64%)	0.99
	7 mg	15 mg	20 mg	30 mg	45 mg	60 mg	
Ropivacaine							
Age, yr	30.2 (4.9)	29.6 (5.5)	29.2 (5.8)	29.4 (5.7)	28.8 (4.8)	28.4 (3.8)	0.87
Weight, kg	66.0 (9.4)	66.0 (7.5)	64.7 (6.7)	66.9 (9.9)	70.9 (9.9)	68.7 (8.2)	0.15
Height, cm	159 (5)	158 (6)	157 (5)	158 (6)	158 (5)	156 (5)	0.65
Cervical dilatation, cm	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–3)	2 (1–2)	1 (1–2)	0.56
Oxytocin use (n)	16 (64%)	19 (76%)	19 (76%)	17 (68%)	16 (64%)	20 (80%)	0.72

Values are mean (SD), median (interquartile range), or number (%).

Table 2. Baseline Pain Scores, Time to Topup, Sensory and Motor Changes, and Incidence of Hypotension

	Dose						*P*
	5 mg	10 mg	15 mg	20 mg	30 mg	40 mg	Value
Bupivacaine							
Baseline VAS Pain score, mm	85 (80–100)	91 (77–100)	83 (77–100)	94 (83–100)	98 (81–100)	92 (79–100)	0.62
Maximum sensory level (dermatome)	L3 (L2.5–L4)	T10 (T7.5–L2.5)	T8 (T7–T10.5)	T7 (T4.5–T9)	T5 (T3.5–T8)	T5 (T4–T8)	<0.001
Maximum Bromage scale motor score	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.40
Time after initial injection to first topup, min	30 (30–31)	31 (30–47)	50 (32–69)	70 (37–98)	81 (36–119)	91 (50–126)	<0.001
Hypotension (n)	0 (0%)	3 (12%)	3 (12%)	4 (16%)	5 (20%)	3 (12%)	0.40
	Dose						
	7 mg	15 mg	20 mg	30 mg	45 mg	60 mg	
Ropivacaine							
Baseline VAS Pain score, mm	100 (80–100)	94 (79–100)	86 (79–100)	93 (85–100)	80 (80–100)	89 (80–100)	0.53
Maximum sensory level (dermatome)	L3 (L2.5–L3.5)	T9 (T6–T11.5)	T8 (T4.5–T11)	T8 (T4–T9)	T7 (T4–T8)	T6 (T3.5–T7)	<0.001
Maximum Bromage scale motor score	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.31
Time after initial injection to first topup, min	30 (30–30)	32 (30–61)	35 (32–88)	80 (33–122)	135 (96–158)	152 (120–181)	<0.001
Hypotension (n)	0 (0%)	3 (12%)	2 (8%)	10 (40%)	8 (32%)	8 (32%)	0.001

Values are median (interquartile range) or number (%).
VAS = Visual Analog Scale.

tients for analgesia in the first stage of labor. Comparison of the two curves showed similar steepness, as evidenced by similar values for the Hill coefficient, but a difference in potency as evidenced by the position of the ropivacaine curve to the right of the bupivacaine curve and the significant difference in ED_{50}. The calculated potency ratio at ED_{50} for ropivacaine:bupivacaine of 0.75 (95% CI 0.65–0.88) was greater than the values previously derived using UDM by Polley *et al.*[1] (0.6 [95% CI 0.49–0.74]) and Capogna *et al.*[2] (0.6 [95% CI 0.47–0.75]), although there is an overlap of 95% CIs between the values in our study and those reported in the previous studies. No difference in potency was apparent at ED_{90} values.

Use of nonsequential random allocation dose–response methodology has a number of advantages and disadvantages compared with UDM, the latter in the recent past having been used more commonly to compare epidural local anesthetics. UDM has gained popularity because it clusters data collection around a specific quantile on the dose–response curve, thereby enabling estimation of the dose or concentration associated with this quantile with a relatively small sample size and without assumptions about the shape of the dose–response curve.[9,10] Usually, the parameter determined is the EC_{50}, which is often referred to as the minimum local anesthetic concentration.[3] UDM can be used to determine other quantiles using methods such as the biased coin design[11] or the Narayana rule,[12] but these have not been described commonly in the anesthetic literature.[13] Results from UDM studies can be easily and simply displayed graphically. However, UDM has a number of important limitations. Estimation of ED_{50} or EC_{50} may be of limited use to clinicians who are more interested in doses at higher quantiles on the dose–response curve. UDM studies provide no information on the shape of the dose–response curve, and UDM studies that are designed to estimate ED_{50} or EC_{50} do not permit accurate inferences about the relative potency of different drugs at quantiles higher (*e.g.*, ED_{90} or EC_{90}) or lower than EC_{50} or ED_{50}, especially if the dose–response curves differ in shape or symmetry. Blinding in UDM may be problematic and because observations are not independent, care needs to be taken to choose appropriate methods of analysis to avoid calculation of spuriously narrow CIs.[14]

In comparison, random allocation studies permit estimation of the shape and position of the entire dose–response curve. The steepness of the dose–response relationship can be

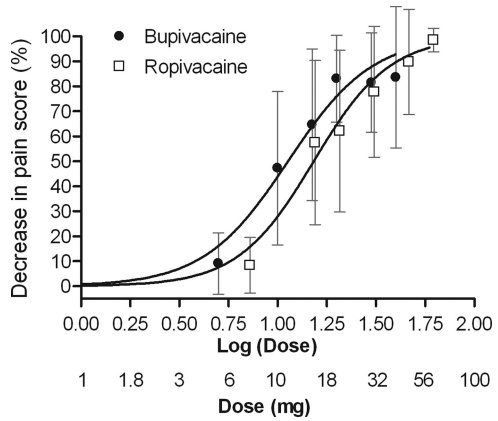

Fig. 2. Variable slope E_{max} sigmoidal dose–response curves for bupivacaine and ropivacaine generated by nonlinear regression. Data points with error bars are shown as mean (SD). The horizontal axis is on a logarithmic scale. Antilog values for dose are shown below log(dose) values to aid interpretation. ED_{50} was defined as the dose of the drug that reduces pain score to 50% of baseline at 30 min, and ED_{90} was defined as the dose of the drug that reduces pain score to 90% of baseline at 30 min. The values for log(ED_{50}) were different for the two local anesthetics, but the values for the Hill coefficient and log(ED_{90}) were similar.

measured and compared, and by interpolation, dose values for any quantile response can be estimated. However, random allocation studies are inherently less efficient than UDM studies for estimating individual target doses. Simulation studies indicate that a sample size of 20–40 subjects in UDM studies will provide stable estimates of a target dose for most realistic scenarios,[10] which is consistent with most UDM articles published in the anesthesia literature.[2,3,15] In contrast, random allocation studies require at least 2 or 3 times more patients or greater[10] and are thus substantially more demanding of time and resources. Furthermore, random allocation studies necessitate the administration of relatively small and large doses to some patients with the resultant potential for inadequate responses and adverse effects, respectively.

In our study, we quantified the response to different doses as the magnitude of change in VAS pain score, normalized to a percentage decrease from the baseline value. Thus, our ED_{50} and other estimates were based on proportional responses averaged among subjects for each dose. In contrast, UDM studies use a binary or quantal outcome or response variable. In some random allocation designs, a binary response is also measured, followed by a linearizing transformation and regression, for example, probit and logit analyses. UDM and other techniques that use a binary outcome require the definition of an "effective" or "successful" response. Historically, such endpoints have been appropriate in toxicology studies in which the endpoint is death or survival. In anesthesia, a binary outcome has been used, for example, to determine minimum alveolar concentration of volatile anesthetics where the outcome is movement or no movement. However, in analgesia studies, the outcome is most often measured on a graded or continuous scale, for example, using a VAS to measure pain scores. In this situation, transformation to a binary outcome involves loss of information regarding the magnitude of response for individual patients and analysis by techniques such as probit or logit analysis is therefore suboptimal.[16] Moreover, definitions of binary outcomes may be somewhat arbitrary and may differ among studies. In studies of labor analgesia, an effective outcome is commonly defined as a VAS pain score of 10 mm or less during a contraction.[2,3,15] Although this outcome is simple and easy to measure, it takes no account of the initial pain score that may vary among subjects. With the availability of suitable computer programs, nonlinear modeling has been recommended as the preferred technique for analyzing graded dose–effect relationships.[17]

For comparative purposes, we performed a secondary analysis of our data in which we converted results into binary responses and then performed probit regression. The calculated values for ED_{50} using this method were similar to those obtained by nonlinear regression but with wider 95% CIs. The potency ratio obtained in the secondary analysis (0.71) was also similar to that obtained in the primary analysis (0.75); however, it should be noted that the 95% CI in the secondary analysis was wide (0.36–1.11), and because this spanned unity, the result was not statistically significant. Mostly likely, the decreased precision of potency estimates in the secondary analysis reflects loss of power associated with

Table 3. Calculated Parameters Derived by Fitting Variable Slope Sigmoidal E_{max} Dose–Response Curves to Datasets for Bupivacaine and Ropivacaine Using Nonlinear Regression

	Bupivacaine	95% CI	Ropivacaine	95% CI
Log(ED_{50})	1.05	1.00–1.10	1.18	1.14–1.23*
ED_{50} (mg)	11.3	10.0–12.7	15.3	13.7–17.1*
Hill coefficient	2.02	1.55–2.50	2.25	1.70–2.79
R^2	0.53		0.59	
Log(ED_{90})	1.52	1.42–1.63	1.61	1.51–1.71
ED_{90} (mg)	33.4	26.2–42.7	40.6	32.4–51.1

ED_{50} was defined as the dose of the drug that reduces pain score to 50% of baseline at 30 min, and ED_{90} was defined as the dose of the drug that reduces pain score to 90% of baseline at 30 min.

* Significant difference between groups, $P < 0.001$.

CI = confidence interval.

Table 4. Results of Dose–Response and Dose-Finding Studies of Epidural Bupivacaine and Ropivacaine for Labor Analgesia

	Bupivacaine, mg	Ropivacaine, mg	Outcome (Response)	Methodology
Columb and Lyons[3]	ED_{50} 13.1 (9.0–17.0)		VAS pain score ≤ 10 mm within 60 min	Up and down
Lyons *et al.*[18]	ED_{50} 13.8 (11.4–16.0)		VAS pain score ≤ 10 mm within 15–60 min	Up and down
Lyons *et al.*[19]	ED_{50} 16.2 (11.0–21.6)		VAS pain score ≤ 10 mm within 30 min	Up and down
Polley *et al.*[20]	ED_{50} 20.8 (18.0–23.4)		VAS pain score ≤ 10 mm within 30 min	Up and down
Camann *et al.*[26]	ED_{50} 24 (12–50)		VAS pain score ≤ 10% of baseline within 30 min	Random allocation and probit analysis
Polley *et al.*[1]	ED_{50} 13.4 (10.4–16.4)	ED_{50} 22.2 (20.0–24.4)	VAS pain score ≤ 10 mm within 30 min	Up and down
Capogna *et al.*[2]	(15.2–22.0)	ED_{50} 31.2 (27.2–35.2)	VAS pain score ≤ 10 mm within 30 min	Up and down
Lee *et al.*[6]		(a) ED_{50} 18.4 (13.4–25.4) (b) ED_{95} 55.9 (35.3–88.5)	VAS pain score ≤ 50% of baseline within 30 min	Random allocation and probit analysis
Palm *et al.*[21]		ED_{50} 26 (24–26)	VAS pain score < 10 mm at 30 min	Up and down
Aveline *et al.*[22]		ED_{50} 19.4 (17.0–21.6)		Up and down
Polley *et al.*[23]	ED_{50} 18.2 (16.2–20.4)		VAS pain score ≤ 10 mm within 30 min	Up and down
Benhamou *et al.*[4]		ED_{50} 18.4 (16.4–20.4)	VAS pain score < 10 mm within 30 min	Up and down
Lyons *et al.*[24]	(a) Bupivacaine 0.125% ED_{50} 17.0 (15.5–18.5) (b) Bupivacaine 0.25% ED_{50} 23.1 (17.2–28.9)		VAS pain score ≤ 10 mm within 30 min	Up and down
Buyse *et al.*[25]	ED_{50} 14.9 (13.4–16.4)		VAS pain score ≤ 15 mm within 30 min	Up and down
Ngan Kee *et al.* (this study)	(a) ED_{50} (D_{50}) 11.3 (10.0–12.7) (b) ED_{90} (D_{90}) 33.4 (26.2–42.7)	(a) ED_{50} (D_{50}) 15.3 (13.7–17.1) (b) ED_{90} (D_{90}) 40.6 (32.4–51.1)	(a) VAS pain score ≤ 50% of baseline at 30 min (b) VAS pain score ≤ 10% of baseline at 30 min	Random allocation and nonlinear regression

For studies using up and down methodology, ED_{50} values were derived from published values for minimum local anesthetic concentration by multiplying concentration by the volume of the injectate. Dose values are in milligrams with 95% confidence intervals in parentheses. Definitions for ED_{50}, ED_{90}, ED_{95}, D_{50}, and D_{90} varied among studies; see text for explanation.

VAS = Visual Analog Scale.

transformation of the graded pain score data to binary outcomes[16]; this is an example of the disadvantages of using this type of outcome.

Results of studies that use a binary outcome have a probabilistic meaning.[10] Thus, ED_{50} or EC_{50} values derived using UDM or logit or probit regression provide an estimate of the dose or concentration at which 50% of the population is likely to respond. In comparison, in investigations such as the current study in which the response is based on a graded or continuous outcome, ED_{50} is an estimate of the dose that is likely to elicit a response of magnitude that is 50% of the maximal response. To avoid confusion, an alternative nomenclature for parameters estimated in studies with graded outcomes is to use the terms D_{50} and D_{90} and so forth rather than ED_{50} and ED_{90}.[17]

Table 4 gives a summary of the results of published dose–response and dose-finding studies of epidural bupivacaine and ropivacaine for labor analgesia, converted to equivalent values for ED_{50}. A wide range of results has been reported. In studies using UDM, the ED_{50} values (minimum local anesthetic concentration) are estimates of the dose (concentration) required to produce a decrease in VAS pain score, most often to ≤10 mm, within 30 min in 50% of patients.[1–4,18–25] In the random allocation dose–response studies using probit analysis, ED_{50} was also calculated as the dose required to produce a decrease in

VAS pain score by a predetermined amount in 50% of patients, but in these studies, the authors chose to use a proportional decrease in VAS pain score (to ≤10% of baseline[26] or to ≤50% of baseline[6] within 30 min) rather than an absolute score as the defined outcome. In comparison, in the current study, ED_{50} is an estimate of the dose required to produce a decrease in VAS pain score of a magnitude of 50% and ED_{90} is an estimate of the dose required to produce a decrease in VAS pain score of a magnitude of 90%. Because of the heterogeneity among these studies, when considering the application of the results of any study to clinical practice, it is important to consider the methodology used and to interpret the outcome determined in appropriate perspective relative to clinical objectives.

We administered all doses in a set volume of 20 ml and described the different groups in terms of mass rather than concentration of drug, the latter being preferred in studies that assess minimum local anesthetic concentration. Although our results are described in terms of ED_{50} and ED_{90}, for comparison with other studies they are easily converted to concentration by dividing values by the volume of each dose. Thus, the equivalent EC_{50} and EC_{90} values derived from our study for bupivacaine are 0.057 (95% CI 0.050–0.064) and 0.167 (0.131–0.214)% wt/vol, respectively, and for ropivacaine are 0.077 (0.069–0.086) and 0.203 (0.162–0.256)% wt/vol, respectively. Also, we described and analyzed doses in terms of drug mass rather than on a molar basis. Because ropivacaine has a smaller molecular weight than bupivacaine, the molar potency ratio for ropivacaine:bupivacaine is slightly less than the value calculated by drug mass.[2]

Of clinical interest, although our results showed a significant difference in potency between bupivacaine and ropivacaine at ED_{50}, the difference at ED_{90} was not significant. This relates to the position of the ED_{90} quantiles on the flat upper portion of the dose–response curves and may explain in part why several clinical studies that have compared single concentrations of bupivacaine and ropivacaine, particularly those that have used a relatively high concentration of 0.25%, have not shown important differences in analgesia or sensory and motor block.[27]

We conducted our study in two phases. The second phase was planned and started after completion and preliminary analysis of the results of the first phase. Unfortunately, this resulted in dose allocation within the study not being fully randomized because the smallest doses of each drug were only given in the second phase. However, all other aspects of conduct of the study were identical for the two phases of the study, and we are aware of no important differences in anesthetic or obstetric management that occurred between the two periods of the study. Nonetheless, we acknowledge that this is a shortcoming of our study.

Finally, our use of nonlinear regression has a number of limitations. Our dose–response curves were derived with the assumption that an E_{max} model was correct and appropriate. The values of the coefficients of determination (R^2) for the derived curves for bupivacaine and ropivacaine were 0.53 and 0.59, respectively, indicating only a moderate goodness of fit. It is possible that other models could also be fitted to the data equally well or better. However, use of an E_{max} model can be justified because it is commonly used to describe drug–receptor interactions.[28] Other random allocation study designs also require assumptions, for example the validity of linear transformations.

In summary, in this study, we used random allocation dose–response methodology to evaluate and compare the analgesic response to epidural bupivacaine and ropivacaine in laboring nulliparous patients. We derived variable slope sigmoidal E_{max} dose–response curves using nonlinear regression and determined that ED_{50} was greater for ropivacaine compared with bupivacaine but ED_{90} and the slopes of the curves were similar.

The authors thank the midwives of the Labour Ward, Prince of Wales Hospital, Shatin, Hong Kong, China, for their assistance and cooperation and John L. Plummer, Ph.D., A.Stat., Chief Medical Scientist, Department of Anaesthesia and Pain Medicine, Flinders University, Bedford Park, Adelaide, South Australia, Australia, for statistical advice for the first phase of the study. Bee B. Lee, M.B.B.S., F.A.N.Z.C.A., F.H.K.A.M., Adjunct Assistant Professor, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Shatin, Hong Kong, China, contributed to the design of the first phase of the study and to data collection in the first phase of the study and Karman K. L. Ng, M.B., Ch.B., F.A.N.Z.C.A., F.H.K.A.M., Adjunct Assistant Professor, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, contributed to data collection in the second phase of the study.

References

1. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ: Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: Implications for therapeutic indexes. ANESTHESIOLOGY 1999; 90:944–50
2. Capogna G, Celleno D, Fusco P, Lyons G, Columb M: Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Br J Anaesth 1999; 82:371–3
3. Columb MO, Lyons G: Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. Anesth Analg 1995; 81:833–7
4. Benhamou D, Ghosh C, Mercier FJ: A randomized sequential allocation study to determine the minimum effective analgesic concentration of levobupivacaine and ropivacaine in patients receiving epidural analgesia for labor. ANESTHESIOLOGY 2003; 99:1383–6
5. Lee BB, Plummer JL, Ngan Kee WD, Ng FF: Dose-response study of epidural bupivacaine and ropivacaine for labor analgesia. Anesth Analg 2005; 100:S-442
6. Lee BB, Ngan Kee WD, Wong EL, Liu JY: Dose-response study of epidural ropivacaine for labor analgesia. ANESTHESIOLOGY 2001; 94:767–72
7. Motulsky HJ, Ransnas LA: Fitting curves to data using nonlinear regression: A practical and nonmathematical review. FASEB J 1987; 1:365–74
8. Motulsky HJ, Christopoulos A: Fitting Models to Biological Data Using Linear and Nonlinear Regression. A Practical Guide to Curve Fitting. San Diego, CA, GraphPad Software Inc., 2003, pp 138–42
9. Dixon WJ, Mood AM: A method for obtaining and analyzing sensitivity data. J Am Stat Assoc 1948; 43:109–26

10. Pace NL, Stylianou MP: Advances in and limitations of up-and-down methodology: A précis of clinical use, study design, and dose estimation in anesthesia research. ANESTHESIOLOGY 2007; 107:144–52
11. Durham SD, Flournoy N, Rosenberger WF: A random walk rule for phase I clinical trials. Biometrics 1997; 53:745–60
12. Ivanova A, Montazer-Haghighi A, Mohanty SG, Durham SD: Improved up-and-down designs for phase I trials. Stat Med 2003; 22:69–82
13. Whitty R, Goldszmidt E, Parkes RK, Carvalho JC: Determination of the ED_{95} for intrathecal plain bupivacaine combined with fentanyl in active labor. Int J Obstet Anesth 2007; 16:341–5
14. Columb MO, Thomson HE: Confidence with confidence intervals. Br J Anaesth 2005; 95:111–2
15. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ, Goralski KH: Relative analgesic potencies of levobupivacaine and ropivacaine for epidural analgesia in labor. ANESTHESIOLOGY 2003; 99:1354–8
16. Fedorov V, Mannino F, Zhang R: Consequences of dichotomization. Pharm Stat 2008; 8:50–61
17. Tallarida RJ: Drug Synergism and Dose-Effect Data Analysis. Boca Raton, Chapman & Hamm/CRC, 2000, pp 173–81
18. Lyons G, Columb M, Hawthorne L, Dresner M: Extradural pain relief in labour: Bupivacaine sparing by extradural fentanyl is dose dependent. Br J Anaesth 1997; 78:493–7
19. Lyons G, Columb M, Wilson RC, Johnson RV: Epidural pain relief in labour: Potencies of levobupivacaine and racemic bupivacaine. Br J Anaesth 1998; 81:899–901
20. Polley LS, Columb MO, Wagner DS, Naughton NN: Dose-dependent reduction of the minimum local analgesic concentration of bupivacaine by sufentanil for epidural analgesia in labor. ANESTHESIOLOGY 1998; 89:626–32
21. Palm S, Gertzen W, Ledowski T, Gleim M, Wulf H: Minimum local analgesic dose of plain ropivacaine *vs.* ropivacaine combined with sufentanil during epidural analgesia for labour. Anaesthesia 2001; 56:526–9
22. Aveline C, El Metaoua S, Masmoudi A, Boelle PY, Bonnet F: The effect of clonidine on the minimum local analgesic concentration of epidural ropivacaine during labor. Anesth Analg 2002; 95:735–40
23. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ: Effect of epidural epinephrine on the minimum local analgesic concentration of epidural bupivacaine in labor. ANESTHESIOLOGY 2002; 96:1123–8
24. Lyons GR, Kocarev MG, Wilson RC, Columb MO: A comparison of minimum local anesthetic volumes and doses of epidural bupivacaine (0.125% w/v and 0.25% w/v) for analgesia in labor. Anesth Analg 2007; 104:412–5
25. Buyse I, Stockman W, Columb M, Vandermeersch E, Van de Velde M: Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. Int J Obstet Anesth 2007;16:22–8
26. Camann W, Abouleish A, Eisenach J, Hood D, Datta S: Intrathecal sufentanil and epidural bupivacaine for labor analgesia: Dose-response of individual agents and in combination. Reg Anesth Pain Med 1998; 23:457–62
27. Writer WDR, Stienstra R, Eddelston JM, Gatt SP, Griffin R, Gutsche BB, Joyce TH, Hedlund C, Heeroma K, Selander D: Neonatal outcome and mode of delivery after epidural analgesia for labour with ropivacaine and bupivacaine: A prospective meta-analysis. Br J Anaesth 1998; 81:713–7
28. MacDougall J: Analysis of Dose-Response Studies—E_{max} Model, Dose Finding in Drug Development. Edited by Ting N. New York, Springer Science + Business Media, Inc., 2006, pp 127–45