The effect of parturient height on the median effective dose of intrathecally administered ropivacaine

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BACKGROUND: Pain during cesarean delivery is one of the more common reasons for a successful medicolegal claim. However, creating an extensive block area can result in hypotension, so determining the precise dose of local anesthetic is critical.

OBJECTIVES: Investigate effects of parturient height on the median effective dose (ED50) of intrathecally-administered ropivacaine.

DESIGN: Prospective cross-sectional analytic study.

SETTING: Anesthesiology department in a provincial hospital in China.

METHODS: Parturients undergoing cesarean delivery under combined spinal and epidural anesthesia were stratified according to height as follows: 150 cm to 155 cm, 156 cm to 160 cm, 161 cm to 165 cm and 166 cm to 170 cm. The spinal component of the anesthetic was established by bolus administration of up-and-down doses of 0.75% plain ropivacaine as determined by the Dixon method. The initial dose of ropivacaine was 5.79 mg and the testing interval dose change was set at 0.75 mg. The block height for the first cold feeling at T5 was considered satisfactory anesthesia.

MAIN OUTCOME MEASURES: ED50 values and vasopressor requirements, nausea, vomiting and shivering.

RESULTS: In 120 parturients, the ED50 for satisfactory block height using intrathecal ropivacaine was 5.92 mg (95% confidence interval[CI] 5.02-6.86 mg) patients of 150 to 155 cm in height; 6.52 mg (95% CI 5.45-7.65 mg) in 156 cm to 160 cm; 7.49 mg (95%CI 6.83-8.25 mg) in 161 cm to 165 cm; 8.35 mg (95%CI 7.55-9.23 mg) in 166 to 170 cm. The ED50 of ropivacaine increased with increasing height of the subject. There were no significant differences in incidence of hypotension, vasopressor requirements, nausea, vomiting and shivering.

CONCLUSION: The ED50 of intrathecal ropivacaine using sensitivity to cold sensation increased with parturient height, indicating that dose may be determined in part by height.

LIMITATION: The ED95 rather than the ED50 for spinal anesthesia is more useful clinically. We did not control for the effect of weight on the dose of local anesthetic. Factors such as baricity, volume, concentration injected, temperature of the solution, and viscosity can affect intrathecal spread of the local anesthetics and block quality.

Pain during cesarean delivery is one of the more common reasons for a successful medicolegal claim. However, creating an extensive block area can result in a significant incidence of hypotension. Maternal hypotension not only presents with distressing symptoms of dizziness, nausea and vomiting, but also impairs placental perfusion and may compromise fetal outcome. Clinical observation confirms that height is a significant variable in predicting the final level of the block. However, some studies also found that adjusting the dose of local anesthetic injected based on differences in
patient height provided no clinically important benefit.\textsuperscript{5,6} Until now, whether the height of parturients affects the dose of local anesthetic is still controversial. Assessing block height by temperature change is considered a reliable method.\textsuperscript{7} A block height to a first cold sensation at T5 is considered satisfactory spinal anesthesia for caesarean delivery.\textsuperscript{8} The height-related ED50 of ropivacaine for block height arrived at by first cold feeling at T5 is an interesting issue and can provide useful information for clinical practice. The aim of this study was to determine the ED50 of intrathecally-administered 0.75% ropivacaine in parturients and to determine the effect of patient height on the dose required for the block height assessed by first cold feeling at T5.

METHODS

This study was approved by the Ethics Committee of Guizhou Provincial People’s Hospital (Guiyang, China). Written informed consent was obtained from all enrolled parturients. This study was conducted at the Department of Anesthesiology, Guizhou Provincial People’s Hospital between December 1, 2013, and December 1, 2015. Eligible subjects were ASA physical status III parturients who had full term (36-41 weeks) singleton pregnancies and were to undergo caesarean delivery, primarily under the spinal component of established combined epidural and spinal anesthesia, with the epidural component to be used if there was need for intraoperative analgesic supplementation or for postoperative analgesia. Parturients with pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, contraindications to spinal anesthesia, those weighing <65 kg or >85 kg, and those taller than 175 cm or shorter than 150 cm were excluded.

Before induction of anesthesia, the authors weighed each parturient and measured her height. The ED50 was determined in subjects stratified according to height as follows: 150 cm to 155 cm, 156 cm to 160 cm, 161 cm to 165 cm and 166 cm to 170 cm. Spinal block was established by bolus administration of up-and-down doses of 0.75% ropivacaine. The first anesthesiologist who performed the anesthesia procedure had more than 18 years of clinical experience and was blinded to the results. The second anesthesiologist who assessed the patients and collected the data was blinded to the intrathecally-administered local anesthetic dose. The third anesthesiologist prepared the study drug, including concentration, volume, and dose, according to the second anesthesiologist’s result of prior parturient.

Parturients were premedicated with oral ranitidine 150 mg the night before surgery. Noninvasive arterial blood pressure, electrocardiogram, and oxygen saturation were monitored (Datex-Ohmeda, Helsinki, Finland). Fluid was given before the spinal block by IV infusion of 500 mL lactated Ringer’s solution. Combined spinal epidural anesthesia was performed with the parturients positioned in the left lateral decubitus to avoid hypotension on a horizontal operating table and palpation of the iliac crests to identify the L3/4 interspace. A 16-gauge Tuohy needle (connected to an air-filled 2-mL syringe) was inserted in this interspace via a midline approach and advanced until its tip entered the epidural space, which was identified by the sudden loss of resistance to air technique. The air injected during identification of the epidural space was <2 mL. After identification of the epidural space, a 25-gauge Whitacre spinal needle was introduced through the Tuohy needle and advanced until clear drops of cerebrospinal fluid (CSF) fell from the spinal needle. At this point, the initial dose of ropivacaine was injected into the subarachnoid space at a rate of 0.1 mL/s (the initial dose of ropivacaine was 0.77 mL, the concentration was 0.75%). The spinal needle was withdrawn, and a 20-gauge epidural catheter was inserted through the Tuohy needle, with the aim of introducing 3 cm of catheter into the epidural space by cephalad-directed Tuohy needle. Immediately after insertion of the epidural catheter, removal of the Tuohy needle, and catheter fixation, the parturient was placed in supine position and then repositioned at the end of the preoperative assessment according to surgical requirements.

The commercially available solution of 0.75% ropivacaine (Naropin, AstraZeneca, Sweden) was used in this study. The concentration of anesthetic solution was kept constant (0.75% ropivacaine) in spinal anesthesia for all parturients, and only the volume was adjusted according to the preceding result. Previous study had found that the intrathecal ED50 for motor block was 5.79 mg for ropivacaine by using up-down analysis,\textsuperscript{9} so the initial dose of local anesthetic solution in our study was 5.79 mg (0.77 mL) and the testing interval dose change was set at 0.75 mg (0.1 mL).

The dose varied according to the up-and-down method for evaluation of the spinal ED50 for local anesthetics.\textsuperscript{10} Up-down sequential allocation is a simple, robust and efficient method of identifying the median effective dose (ED50) or concentration (EC50). The dose received by a subject is determined by the response of the previous subject. Depending on the outcome of interest a binary (yes/no) outcome is defined. If the outcome is effective, the dose for the subsequent subject is decreased, while if ineffective it is increased. Using this approach, testing is eventually centred about the eventual EC50 or ED50. The dose-response relation-
ship is defined with the greatest precision at the ED50, which is the point at which pharmacological potency is defined. Changes in ED50 should therefore allow the local anesthetic sparing effect of other co-analgesics and the effects on requirements due to non-pharmacologic or obstetric factors to be calculated. The dose of ropivacaine was increased or decreased by 0.75 mg for the next parturient according to whether the block height of previous parturient arrived at T5 or not. The efficacy of the administered ropivacaine dose was assessed by the block height at T5 using a sensation of cold for each parturient. The block height for the first cold feeling at T5 was considered satisfactory spinal anesthesia for caesarean section. Five minutes after the injection of spinal anesthetic, ice was applied above the parturient’s clavicle as a reference and then applied to the L1 dermatome, asking the parturient “Can you feel cold?”, if the parturients stated that they could not feel anything, the ice was moved continuously in the cephalad direction in the mid-clavicular line until they reported they first felt the cold, and the level of block height was recorded.

The block heights were assessed and recorded when the anesthesiologist considered that the parturient had a satisfactory spinal anesthesia block for surgery to proceed. Anesthesiologists also recorded whether the parturient reported discomfort or needed an analgesic/anesthetic intervention by epidural catheter at any time during surgery, as well as the time of intervention. Those patients missing assessments because they were discharged from hospital were followed up over the telephone at home.

Mean arterial blood pressure and heart rate were recorded at baseline and then measured at 2 min intervals, starting 2 min after the spinal injection and continuing until the start of surgery, after which recordings were made at 5 min intervals. Hypotension was defined as a 20% decrease in the mean arterial blood pressure compared to the baseline values and treated, if necessary, with 5 mg IV boluses of ephedrine. Nausea, vomiting and shivering episodes were observed during operation. The incidence of hypotension, vasopressor requirements, nausea, vomiting and shivering was recorded.

**Statistical analysis**

Statistical analysis was performed using SPSS 17.0 for windows (SPSS Inc., Chicago, IL). Data are expressed as mean (standard deviation), median (range), and count as appropriate. Demographic data were collected and presented as mean (SD). Means (SD) were analyzed using one-way analysis of variance, and the least significant difference method was used for multiple comparison tests among groups. Counts were analyzed using the Fisher exact test. The ED50 was estimated from the up-and-down sequences using the method of Dixon and Massey and probit regression. The ED50 was analyzed using analysis of variance and followed by post hoc pairwise comparisons with Bonferroni correction. The mean dosage was determined from the midpoints of all independent pairs of patients involving a crossover from failure to success. According to the study by Paul and Fisher, parturients were enrolled until 4 pairs were obtained. \( P < .01 \) was considered statistically significant.

**RESULTS**

Of 150 parturients screened, all 120 parturients completed the study and were included in the analysis. Thirty-one were excluded. Demographic and obstetric data were similar in the groups (Table 1). Sensory block was achieved within 5 min after intrathecal-ad-
Administration of ropivacaine in all patients. Analgesia was adequate for surgery in all patients, and all enrolled patients successfully completed surgery. No patient had headache after the operation, and no patient required general anesthesia.

The sequences of effective and ineffective outcomes are presented in Figure 1. Using the formula of Dixon and Massey, the ED50 for the block height arrived at T5 using cold in a standardized manner is shown in Table 2 and Figure 2.

Incidences of analgesia supplementation by epidural catheter, hypotension, vasopressor requirements, nausea, vomiting and shivering were recorded (Table 3). Routine observations were similar in all groups for maternal ECG, heart rate, pulse oximetry values, and fetal heart rate tracings.

**DISCUSSION**

To our knowledge, this is the first study in which the ED50 for the block height of 0.75% ropivacaine was stratified by parturient's height. Up-down designs can be use as robust estimators of the ED50, but points beyond the ranges of dose actually tested, such as the ED95, should be estimated with caution. Such extrapolation can underestimate the true ED95. However, such estimates may be useful to guide further research. Moreover, as a guide to clinical practice, it is advisable on safety grounds to underestimate rather than overestimate the likely ED95.13

In our study, the ED50 of intrathecal ropivacaine for the block height arrived at T5 using sensitivity to cold feeling was 5.92 mg in 150 to 155 cm group and the dose increased to 8.35 mg in 166 to 170 cm; ED50 of ropivacaine increased with increasing height for parturients. Common sense and clinical experience tell us, nevertheless, that injection of a local anesthetic solution at L3/4 interspace in a short patient is associated with a more cephalad spinal segmental level of anesthesia than is injection of the same amount of the same anesthetic injected in the same way in a tall patient. One reason for this is that even if the anesthetic solution were to spread to an equal extend (such as 10 cm), from the site of injection in both the tall and the short patient, a 10 cm spread will reach a higher spinal segmental level in the short patient than it will in the tall patient. An additional reason for lower segmental levels of anesthesia in taller patients than in shorter patients is that the local anesthetic solution that spreads a distance (such as 10 cm) from the site of injection in a short patient may not spread the same distance, 10 cm, in a tall patient. It may not spread as far in the tall patient because of height-related difference in spinal
Table 2. ED50 values for the block height arrived at T5 using cold sensation as calculated by up-down and probit regression analyses.

|                  | 150-155 cm (n=30) | 155-160 cm (n=30) | 160-165 cm (n=30) | 165-170 cm (n=30) |
|------------------|-------------------|-------------------|-------------------|-------------------|
| **Up-Down**      |                   |                   |                   |                   |
| ED50 (mg)        | 5.92±4.99-6.93    | 6.52ab 5.39-7.71  | 7.49abc 6.79-8.31 | 8.35c 7.52-9.29   |
| 99% CI           |                   |                   |                   |                   |
| **Probit**       |                   |                   |                   |                   |
| regression       | 6.01ab 5.11-6.94 | 6.75ab 6.50-7.78  | 7.54c 6.95-8.42   | 8.44c 7.62-9.40   |
| ED50 (mg)        |                   |                   |                   |                   |
| 99% CI           |                   |                   |                   |                   |

One-way ANOVA, P=.007. Bonferroni multiple comparison, a150-155cm vs 155-160cm, P=.008; b155-160cm vs 160-165cm, P=.005; c160-165cm vs 165-170cm, P=.006. Regression model: R=0.644, Rsqr=0.414, Adj Rsqr=0.409, F=83.431, P<.001. Data are reported as mean and standard, and results shown as median effective dose (99% confidence interval).

Table 3. Incidences of hypotension, vasopressor requirements, nausea, vomiting and shivering.

|                  | 150-155 cm (n=30) | 155-160 cm (n=30) | 160-165 cm (n=30) | 165-170 cm (n=30) |
|------------------|-------------------|-------------------|-------------------|-------------------|
| Hypotension      | 3                 | 2                 | 5                 | 5                 |
| Nausea/Vomiting  | 3                 | 2                 | 2                 | 1                 |
| Shivering        | 4                 | 5                 | 3                 | 4                 |
| Ephedrine        | 6.87 (4.65)       | 8.01 (5.23)       | 7.85 (3.32)       | 5.54 (4.01)       |
| requirements (mg)| (mean and standard deviation) |                   |                   |                   |

The statistics for hypotension, nausea/vomiting and shivering were analyzed using rank-sum test and the statistic for ephedrine requirements was analyzed using one-way analysis of variance. No significant differences among different groups (All P>.48).

CSF volume. The volume of CSF below the termination of cord at L2 is greater in tall than in short subjects because the length of the cauda equine is greater. The initial volume of CSF into which the local anesthetic is injected at L3/4 being greater, there will be greater dilution of the anesthetic solution at the site of injection and therefore less cephalad spread in the taller patient. The volume of CSF above termination of the cord at L2 may also be greater in tall patients than in short patients. The diameter of the spinal cord is greater in taller patients than in shorter patients. So, too, is the depth of the subarachnoid space, i.e., distance from dura to pia mater. Although the ratio between depth of subarachnoid space and diameter of the cord remains constant regardless of height, there is, however, a slight increase in absolute volume of CSF at any given level of the cord due to the increase in depth of the subarachnoid space. The increase in volume of CSF above L2 in taller patients would further dilute local anesthetic solution injected at L3/4 and so be a contributory factor to the lower levels of anesthesia observed in taller patient. The effect was also studied by Harten,14 in which the authors adjusted the dose regimen of hyperbaric 0.5% bupivacaine according to the height of parturients and found a dose of bupivacaine calculated according to parturients’ height can decrease incidence and severity of maternal hypotension and ephedrine requirement as well as lower the incidence of high spinal block, compared to a fixed dose group. Pargger et al also found that height significantly contributed to the spread of anesthesia.15 Our study further improved understanding of the relationship between parturients’ height and local anesthetic dosage. However, some studies found that height may have some small influence on the spread of sensory block; the variation in spread of block within patients of the same height is large, and parturient height does not affect the spread of hyperbaric spinal anesthesia.16-18 The reason for inconsistency may be that ED50 is the concept of minimum local anesthetic dosage. The height of the parturient has an effect on dose at lower doses of local anesthetic; but it is also true that at higher doses, usually used clinically, the differences tend to be undetectable.

There were some limitations in this study. First, in clinical practice, the anesthesiologist is not interested in the ED50 for spinal anesthesia, but more likely the ED95. However, the issue of ED50 versus ED95 is more important for spinal anesthesia than epidural
anesthesia since in many cases spinal anesthesia will be a “one-shot” affair so the dose has to be enough. Second, clinical observation confirms that weight is a significant variable in predicting the final level of the block, so the weight of subjects enrolled in our study was >65kg and <85kg, but we did not control for the effect of weight on the dose of local anesthetic. The body mass index of subjects stratified according to height decreased with increased height in our study. The theory is that obese patients may have an increased volume of fat in the extradural space which is responsible for a reduction in the volume of cerebrospinal fluid. The parturients with higher body mass index need fewer doses of ropivacaine, but we did not consider this effect when we designed the study. Third, other factors such as baricity, volume, concentration injected, temperature of the solution, and viscosity affect intrathecal spread of the local anesthetics and block quality. In addition, plain ropivacaine was used in our study; a previous study demonstrated that plain local anesthetics exhibit greater variability in effect and are less predictable, so that the block may be over or underestimated, so the results in our study might be affected by these unpredictable elements. However, the height of parturients is a useful reference index for a given amount of local anesthetic.

In conclusion, because the ED50 of intrathecal ropivacaine for the block height arrived at T5 using sensitivity to cold feeling increased with height, it demonstrates that height may have an effect on ED50 of intrathecal ropivacaine.

Conflict of interest
The authors report no conflict of interest.

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