Original article

Minimum effective local anesthetic dose of intrathecal hyperbaric ropivacaine and bupivacaine for cesarean section

GENG Zhi-yu, WANG Dong-xin and WU Xin-min

Background   Intrathecal anesthesia is commonly used for cesarean section. Bupivacaine and ropivacaine have all been used as intrathecal drugs. The minimum effective local anesthetic dose (MLAD) of intrathecal ropivacaine for nonobstetric patients has been reported. However, few data are available on the MLAD of hyperbaric ropivacine for obstetric patients and the relative potency to bupivacaine has not been fully determined. In this study, we sought to determine the MLAD of intrathecal ropivacaine and bupivacaine for elective cesarean section and to define their relative potency ratio.

Methods   We enrolled forty parturients undergoing elective cesarean section under combined spinal-epidural anesthesia and randomized them to one of two groups to receive intrathecal 0.5% hyperbaric ropivacaine or bupivacaine. The initial dose was 10 mg, and was increased in increments of 1 mg, using the technique of up-down sequential allocation. Efficacy was accepted if adequate sensory dermatomal anesthesia to pin prick to T7 or higher was attained within 20 minutes after intrathecal injection, and required no supplementary epidural injection for procedure until at least 50 minutes after the intrathecal injection.

Results   The intrathecal MLAD was 9.45 mg (95%confidence interval (*CI*), 8.45–10.56 mg) for ropivacaine and 7.53 mg (95%*CI*, 7.00–8.10 mg) for bupivacaine. The relative potency ratio was 0.80 (95% *CI*, 0.74–0.85) for ropivacaine/bupivacaine when given intrathecally in cesarean section.

Conclusion   Ropivacaine is 20% less potent than bupivacaine during intrathecal anesthesia for cesarean delivery.

Chin Med J 2011;124(4):509-513

Ropivacaine is the first pure S-(-) enantiomer amino-amide local anesthetic agent with structural and pharmacodynamic similarity to bupivacaine. It is considered to block sensory nerves to a great degree than motor nerves. The drug is less cardiotoxic than equivalent concentrations of racemic bupivacaine *in vitro* and has a significantly higher threshold for central nervous system toxicity than racemic bupivacaine. And 0.5% ropivacaine has been registered for intrathecal use.[1,2]

Several recent reports have described the intrathecal use of ropivacaine for obstetric and nonobstetric patients.[3-7] Many investigators have reported ropivacaine to be less potent than bupivacaine. In a previous dose-response study with plain ropivacine for cesarean delivery, Khaw et al[6] confirmed that the 95% effective dose (ED$_{95}$) was 26.8 mg ((95% confidence interval (*CI*), 23.6–34.1 mg). The minimum effective local anesthetic dose (MLAD) of intrathecal ropivacaine for nonobstetric patients has been reported.[8] However, few data are available on the MLAD of hyperbaric ropivacine for obstetric patients. Data from nonobstetric patients cannot be directly extrapolated to obstetrics because of lower dose requirements.

The aim of this prospective, randomized study was to determine the MLAD for intrathecal hyperbaric ropivacaine and bupivacaine, and then to estimate the potency ratio of these two drugs. For this purpose, we used the up-down sequential allocation model,[9] which allows the MLADs for intrathecal local anesthetics to be estimated.

METHODS

Study design and patients recruitment

This prospective, randomized, double-blinded up-down sequential allocation study was approved by the Ethics Committee of Peking University First Hospital, and written informed consent was obtained from all patients. Forty full-term singleton parturients scheduled for elective cesarean delivery under combined spinal-epidural anesthesia (CSE) were enrolled in the study. Inclusion criteria were ASA physical status I or II, age 20–40 years, body weight <85 kg, and height 150–170 cm. Exclusion criteria were known hypersensitivity to amide local anesthetics, contraindications to spinal or epidural anesthesia, parturients who had obstetric complications or evidence of fetal compromise.

Department of Anesthesiology and Surgical Intensive Care, Peking University First Hospital, Beijing 100034, China (Geng ZY, Wang DX and Wu XM)
Correspondence to: Dr. GENG Zhi-yu, Department of Anesthesiology and Surgical Intensive Care, Peking University First Hospital, Beijing 100034, China (Tel: 86-10-83572632. Fax: 86-10-66551796. Email: gengzhiyu_2005@yahoo.com.cn)

All patients received no premedication. Standard monitoring included continuous electrocardiogram, pulse oximetry, and noninvasive measurement of arterial blood pressure. Intravenous access was secured in the forearm and 10 ml/kg of Ringer's lactate solution was infused for 15 minutes before the initiation of the block. The epidural space was located using a 16-gauge Tuohy needle and loss of resistance to saline technique at the L2-3 interspace, with the women in the right lateral position. After the sighting of cerebrospinal fluid (CSF) in the hub of a 27-gauge pencil-point needle passed through the Tuohy needle, the study drug was injected into the intrathecal space in 20 seconds. The spinal needle was then withdrawn, and an epidural catheter was threaded through the epidural needle. Parturients were then immediately turned supine with left uterine displacement. The patients were randomized to one of two groups, by using a computer-generated list, to receive an intrathecal injection of either 0.5% hyperbaric ropivacaine or bupivacaine in 5% glucose. The hyperbaric ropivacaine solutions were prepared aseptically immediately before injection with equal volumes of 1% (wt/vol) ropivacaine (Naropin, AstraZeneca, Sweden) and 10% (wt/vol) dextrose. The hyperbaric bupivacaine solutions were prepared with 2:1 volume of 0.75% (wt/vol) bupivacaine and 10% (wt/vol) dextrose. Preliminary analysis in our laboratory showed that the specific gravity at 23°C of these solutions was 1.027 and 1.020 respectively.

The preliminary dose of the local anesthetic solution was 10 mg and the testing interval was set at 1 mg for both groups. The dose of the drug in each group was determined by the outcome in the previous parturient, according to the up-down sequential allocation technique. An effective dose was defined as a dose that provided adequate sensory dermatomal anesthesia to pinprick to T7 or higher and required no supplementary epidural injection for surgery proceeded successfully until at least 50 minutes after the intrathecal injection. Otherwise, the epidural catheter was topped up by using 2% (wt/vol) lidocaine given in incremental doses until adequate dermatomal anesthesia was obtained. Patients who complained of intraoperative pain with moderate to severe discomfort were treated with fentanyl 0.1 mg. If pain remained intolerable, with a score of 7 or more on an 11-point numerical scale (0=no pain and 10=most severe pain) after fentanyl, the epidural was topped up. For patients requiring epidural top-up, the spinal anesthesia was classified as ineffective.

Assessment and data collection
Sensory and motor assessments were performed at 2-minute intervals for the first 30 minutes. Thereafter, the blocks were assessed at 15-minute intervals until the end of surgery. Results of the pinprick test were determined bilaterally at midclavicular level by using a short-beveled 27-gauge needle. Motor block in the lower limb was assessed by a modified Bromage scale (0=no paralysis, 1=unable to raise extended leg, 2=unable to flex knee,

3=unable to flex ankle). All of the assessments were made by an anesthetist who was blinded to the group assignment as well as to the drug injected.

The quality of abdominal muscle relaxation was evaluated by the surgeon at the end of the surgery as excellent (no disturbing muscle strain), satisfactory (disturbing, but acceptable muscle strain), or unsatisfactory (unacceptable muscle strain).

Baseline blood pressure and heart rate values were recorded before the preanesthetic infusion. The values were recorded before the induction every 2 minutes before delivery, and then 5 minutes until discharge from the recovery room. Arterial oxygen saturation was continuously monitored by pulse oximetry throughout surgery. Hypotension (defined as systolic blood pressure <90 mmHg or a decrease>30% from baseline) was treated with IV ephedrine 6mg and additional lactated Ringer's solution. Maternal bradycardia (defined as heart rate <50 beats/min) was treated with IV atropine 0.3 mg. Nausea or vomiting was treated with intravenous ondansetron 4 mg. Oxygen was routinely administered via a face mask at the flow rate of 5 L/min until the end of surgery.

All patients were followed up at 24 hours after surgery, with instructions to report the side effects including headache, back pain, and transient neurological symptoms.

Statistical analysis
Demographic and obstetric data were presented as mean ±standard deviation (SD) and analyzed using Student's *t* test. The up-and-down sequences were estimated using the method of Dixon and Massey, which enabled MLAD with 95% *CI* to be derived.[9] Analyses were performed using the SPSS14.0 software. Statistical significance was defined for an overall α error at the 0.05 level. All *P* values were two-sided.

RESULTS

Demographic data
The patients' characteristics are presented in Table. Demographic and obstetrical data were similar in the groups.

Table. Demographic and surgical data (mean±SD, *n*=20)

Variables	Ropivacaine	Bupivacaine
Age (years)	31.0±3.1	31.4±4.2
Height (cm)	162.0±6.2	161.0±3.4
Weight (kg)	71.4±6.4	73.8±6.4
Gestation (weeks)	39.2±1.3	39.4±1.2
Duration of surgery (minutes)	46.0±11.0	42.0±10.0

Outcomes
The sequences of effective and ineffective outcomes are shown in Figure. The intrathecal MLAD of ropivacaine was 9.45 mg (95%*CI*, 8.45–10.56) and that of bupivacaine
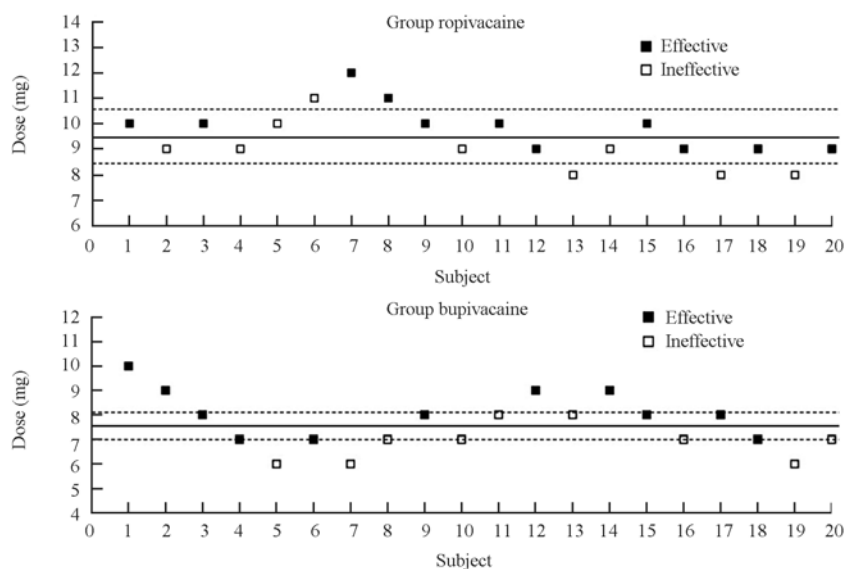
Figure. Sequences of effective and ineffective outcomes. As assessed using up-down analysis the intrathecal MLAD of ropivacaine was 9.45 mg (95%*CI*, 8.45−10.56) and that of bupivacaine was 7.53 mg (95%*CI*, 7.00−8.10).

was 7.53 mg (95%*CI*, 7.00–8.10). The relative potency ratio of ropivacaine: bupivacaine was 0.80 (95%*CI*, 0.74–0.85). Anesthesia was successful by the predetermined criteria in 11 patients in both groups.

Five patients in ropivacaine group (5/20) and six patients in bupivacaine group (6/20) required ephedrine for correction of hypotension during surgery. Three patients in each group required ondansetron for correction of vomiting. The incidence of hypotension, consumption of ephedrine and episodes of nausea and vomiting were similar between groups.

In all 11 patients who had successful anesthesia in the ropivacaine group, ten patients (10/11) had motor block, seven patients had complete motor block with Bromage score 3 and three patients had incomplete motor block with Bromage score 1 at the end of surgery. In the bupivacaine group, all patients (11/11) of successful anesthesia had complete motor block with Bromage score 3 at the end of surgery. No patients reported residual neurologic changes or back pain at 24 hours after surgery.

DISCUSSION

The concept of minimum local anesthetic concentration has been established to determine the median effective concentration and relative potencies of local anesthetics for spinal and epidural anesthesia.[10] More recently, the median effective dose has been developed to assess the minimum effective anesthetic dose of local anesthetics for continuous spinal anesthesia.[8]

In this study, we assessed the minimum effective local anesthetic dose (MLAD) of hyperbaric ropivacaine and bupivacaine and established the potency ratio for these two drugs when administered by the intrathecal route. We found that the intrathecal MLAD for ropivacaine was 9.45 mg (95%*CI*, 8.45–10.56) and that of bupivacaine was 7.53 mg (95%*CI*, 7.00–8.10), and spinal ropivacaine

was 20% less potent than bupivacaine.

Ropivacaine was the first local anesthetics marked as pure S-(-) enantiomer and it is found to have the best safety profile of all long-acting local anesthetics. The S-enantiomer ropivacaine produce less motor block than racemic bupivacaine by the epidural route. Lacassie et al[11] found the epidural potency ratio of motor block for ropivacaine/bupivacaine to be 0.66. Polley et al[12] described ropivacaine as 40% less potent than bupivacaine for labor epidural analgesia.

The greater lipid solubility of bupivacaine becomes more apparent in the intrathecal space near the spinal cord, and this means greater partition into the cord with almost inevitable motor-blocking effects. It is noteworthy, however, that the sensory-motor separation observed with intrathecal ropivacaine studies is not remarkable when compared with that of previous epidural studies.[3-6,13] Thus, it appears that any advantages due to sensory-motor separation are reduced to some extent with intrathecal administration. We have shown in this study that among eleven successful patients of ropivacaine group, 90% patients had motor block at the end of surgery.

In a previous dose-response study with plain spinal ropivacine for cesarean delivery, Khaw et al[6] determined the ED_{50} to be 16.7 mg (95%*CI*, 14.1–18.8) and ED_{95} to be 26.8 mg (95%*CI*, 23.6–34.1). In another study, Celleno et al[14] showed that the ED_{50} of plain ropivacaine for cesarean section using up-down sequential method was 14.22 mg. It should be noted that the ED_{50} of ropivacaine reported in these studies seems to be higher than the MLAD found in our study.

We attributed this difference to be density of ropivacaine solutions administered intrathecally. The ropivacaine solution used in this study was hyperbaric whereas those used in other studies above were plain or hypobaric. The characteristics of the neuraxial block during spinal

anesthesia are influenced by the interaction among baricity, gravity, and patient position. It was observed previously that when intrathecal injection was performed with patients in the lateral position, hyperbaric solution tended to give a higher cephalic spread, whereas plain solutions frequently resulted in insufficient cephalic spread of anesthesia.[15] Usually, glucose-free solutions are marginally hypobaric and have been found previously to be unpredictably spread and have a higher frequent incidence of insufficient cephalic spread requiring supplementary anesthesia or conversion to general anesthesia. Many studies showed that hyperbaric solutions produced spinal anesthesia with faster onset and recovery, less variation in maximum sensory and motor block and might enable a smaller dose to be used compared with plain solutions.[3-5,16]

In the other recent dose-response study of hyperbaric ropivacaine for cesarean delivery, Chen et al[17] determined the ED_{50} to be 10.37 mg (95%*CI*, 5.23–11.59) and ED_{95} to be 15.39 mg (95%*CI*, 13.81–23.59) in Chinese parturients. Their results are consistent with ours in spite of the minor difference that spinal anesthesia was performed at L2-3 interspace in our study, while at L3-4 interspace in Chen's study.

In two previous studies, Camorcia et al[18,19] used up-down sequential allocation method to compare the analgesic and motor-blocking efficacies of intrathecal ropivacaine and bupivacaine for labor analgesia. The intrathecal minimum local analgesic dose was 3.64 mg (95%*CI*, 3.33–3.96) for ropivacaine and 2.37 mg (95%*CI*, 2.17–2.58) for bupivacaine in the first stage of labor, the relative analgesic potency ratio was 0.65 (0.56–0.76) for ropivacaine: bupivacaine. The intrathecal ED_{50} for motor block was 5.79 mg (95%*CI*, 4.62–6.96) for ropivacaine and 3.44 mg (95%*CI*, 2.55–4.34) for bupivacaine in cesarean delivery, the relative motor blocking potency ratio was 0.59 (0.42–0.82) for ropivacaine: bupivacaine.

In this study we found that the relative potency ratio was 0.80 (95%*CI*, 0.74–0.85) for ropivacaine: bupivacaine, this difference may be due to several factors. First, the above previous studies used 0.25% or 0.50% glucose-free solutions of ropivacaine and plain ropivacaine resulted in lesser cephalic spread, slower onset of analgesia and lower maximal extent of sensory and motor block in comparison with hyperbaric solutions.[3,5,16] Second, the definition of adequate block in our study was different from those in previous studies which may influence the results of ED_{50}. Lee et al[20] used up-down sequential allocation method to determine the relative potency ratio of intrathecal ropivacaine/bupivacaine in lower limb surgery. A success was recorded if a bilateral T12 sensory block to cold was attained within 20 minutes after intrathecal injection and the relative anesthetic potency ratio was 0.65 (95%*CI*, 0.54–0.80) for ropivacaine/ bupivacaine.

We defined sufficient anesthesia for cesarean delivery as a dose that provided adequate sensory dermatomal anesthesia to pinprick to T7 dermatome. For cesarean delivery, it has been purposed that to achieve optimum conditions for surgery, one should aim to achieve an upper level of sensory anesthesia of T4.[21] But in previous study, T7 is an optimum anesthesia level which can provide good condition for cesarean section and higher block height probably resulted in the increased incidence of hypotension.[16,17]

In conclusion, we found that the MLADs of intrathecally hyperbaric ropivacaine and bupivacaine for cesarean delivery were 9.45 mg (95%*CI*, 8.45–10.56) and 7.53 mg (95%*CI*, 7.00–8.10) respectively. Our results suggested that spinal ropivacaine was 20% less potent than bupivacaine.

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