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Original Article

Relative potency ratio between hyperbaric and isobaric solutions of ropivacaine in subarachnoid block for knee arthroscopy

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Abstract: Objective: To observe the potency ratio of hyperbaric to isobaric solutions of ropivacaine in subarachnoid block for knee arthroscopy. Methods: Fifty patients receiving knee arthroscopy under combined spinal-epidural anesthesia were randomly divided into isobaric ropivacaine group and hyperbaric ropivacaine group (0.5% ropivacaine, prepared with equal volume of 10% glucose and 1% isobaric ropivacaine). Successful criteria of spinal anesthesia were (1) a bilateral loss of pinprick sensation at or above the level of T12; (2) adequate motor block during knee arthroscopy (modified Bromage's score ≥2); and (3) no requirement of additional epidural administration at least within 60 min after intrathecal injection. Drug consumption was determined with up-and-down method, and then ED_{50} was calculated. Results: The ED_{50} of isobaric ropivacaine was 9.71 mg (95% CI 8.11-11.32), and the ED_{50} of hyperbaric ropivacaine was 6.55 mg (95% CI 6.07-7.04), and the relative potency ratio was 0.67 (95% CI 0.56-0.80) for hyperbaric/isobaric ropivacaine. Conclusions: The ED_{50} of hyperbaric ropivacaine is less than that of isobaric ropivacaine in subarachnoid block anesthesia for knee arthroscopy.

Keywords: Subarachnoid block anesthesia, ropivacaine, hyperbaric solution

Introduction

In subarachnoid block anesthesia, hyperbaric solution of ropivacaine is well known to have a more predictable and reliable block, and higher success rate than that of isobaric solution of ropivacaine. Whiteside et al [1] reported that 3 ml of 0.5% hyperbaric ropivacaine prepared with equal volumes of 10 mg/ml ropivacaine and 100 mg/ml glucose produced the same reliable spinal anesthesia, and exhibited faster disappearance of nerve block as compared to 3 ml of 0.5% bupivacaine. Kallio et al [2] also reported that intrathecal 15 mg of hyperbaric ropivacaine prepared with 1.5 ml of 1% ropivacaine and 0.5 ml of 30% glucose solution had faster effect onset, higher success rate at or above the level of T10 and faster disappearance of nerve block as compared to 2 ml of isobaric ropivacaine (7.5 mg/ml). Lee et al [3] determined ED_{50} and ED_{95} of intrathecal ropivacaine prepared by mixture of various doses of isobaric ropivacaine and saline. However, until now ED_{50} has not been compared between hyperbaric ropivacaine and isobaric ropivacaine. The aim of this study was to prove our hypothesis that ED_{50} of hyperbaric ropivacaine may be lower than that of isobaric ropivacaine when they achieve the same anesthetic effect.

Materials and methods

All study methods were approved by the Ethics Committee of Beijing Jishuitan Hospital. All the subjects enrolled into the study gave written formal consent to participate.

Subjects

Fifty patients (ASA I-II) aged 18-60 years who underwent selective knee arthroscopy under combined spinal-epidural anesthesia were enrolled in the prospective, randomized and double-blind study. The patients with cardiac disease, respiratory disease, allergy to amide-type local anesthetics, peripheral neuropathy and contraindications to spinal and epidural anesthesia were excluded from this study.

Table 1. Demographics and duration of surgery in isobaric ropivacaine group and hyperbaric ropivacaine group ($\bar{x} \pm s$)

	Isobaric ropivacaine group (n=25)	Hyperbaric ropivacaine group (n=25)
Age (years)	31.9 ± 8.4	32.2 ± 7.9
Gender (M/F)	20/5	19/6
Weight (kg)	71.1 ± 15.1	68.7 ± 13.8
Height (cm)	171.3 ± 7.6	173.1 ± 8.8
ASA (1/2)	21/4	22/3
Duration of Surgery (min)	41.4 ± 10.8	38.6 ± 11.9

Notes: M: male; F: female.

Anesthesia

In the operating room, standard monitoring including electrocardiogram, noninvasive arterial blood pressure and pulse oximetry was performed. All patients received 500 ml of Lactated Ringer's Solution before the spinal anesthesia. Oxygen of 2 L/min was given through nasal catheter during anesthesia and operation. The patients were randomly divided into isobaric ropivacaine group (n=25) and hyperbaric ropivacaine group (n=25) according to a computer generated list. Isobaric ropivacaine (0.5%, density of 0.9998 at 23°C) was prepared with equal volumes of 1% ropivacaine (Naropin, AstraZeneca Pty, Soterlaje, Sweden) and 0.9% normal saline, and was used in isobaric ropivacaine group. Hyperbaric ropivacaine (0.5%, density of 1.0199 at 23°C) was prepared with equal volume of 10% glucose solution and 1% ropivacaine, and was used in hyperbaric ropivacaine group. A combined spinal-epidural technique was performed at the L3-4 interspace of patients in the lateral position. The epidural space was identified with a 17-gauge Tuohy needle by the loss of air resistance, and then a 25-gauge Whitacre spinal needle was put through the Tuohy needle. After free flow of cerebrospinal fluid was confirmed, ropivacaine was administered through the Whitacre spinal needle toward the direction of the head. And the Whitacre spinal needle was replaced by a 3 cm-long epidural catheter. No local anesthetics were injected via the epidural catheter. The patients immediately returned to supine position.

Assessment

An independent anesthetist who was unaware of the study performed sensory and motor block evaluations. Sensory block was evaluated by testing bilateral loss to pinprick sensation, and motor block was assessed according to the modified Bromage Scale [4] (0=no block, able to flex hip, knees, and ankles; 1=able to move knee joint, unable to do straight leg raising; 2=able to flex ankle joint, unable to flex knees; 3=inability to move hip, knees, and ankles). Successful criteria of spinal anesthesia were [5] (1) a bilateral loss of pinprick sensation at or above the level of T12; (2) adequate motor block during knee arthroscopy (modified Bromage's score ≥2); and (3) no requirement of additional epidural administration at least within 60 min after intrathecal injection. According to the up-down sequential allocation [6], the initial dose of ropivacaine was 12 mg in both hyperbaric ropivacaine group and isobaric ropivacaine group, and the increment or decrement in the dose of ropivacaine was set at one milligram based on an effective or an ineffective response of the previous patient. Hypotension was defined as that the systolic arterial pressure was decreased to <90 mmHg or <70% of preoperative blood pressure, and was treated by intravenous 5 mg bolus of ephedrine. When heart rate was less than 60 beats per minutes, intravenous 0.5 mg bolus of atropine was given. Any adverse effects including nausea, vomiting, headache, backache and neurological symptoms were recorded.

Statistical analysis

Demographic data were presented as number or ($\bar{x} \pm s$). The age, height, weight and the duration of surgery were analyzed using unpaired *t*-test. Sex and ASA physical status were analyzed using X^2 test. Values of ED_{50} were analyzed using the method of Dixon and Massey [7]. A sample size of 25 patients for each group was determined based on the outcome of previous study [8]. Statistical significance was established at P <0.05. Analyses were performed with SPSS 15.0 for Windows (SPSS, Chicago, IL) and Excel 2003 (Microsoft Corporation, Redmond, WA).

Results

Complete data of the 50 patients were obtained in this study. Demographics and surgical dura-

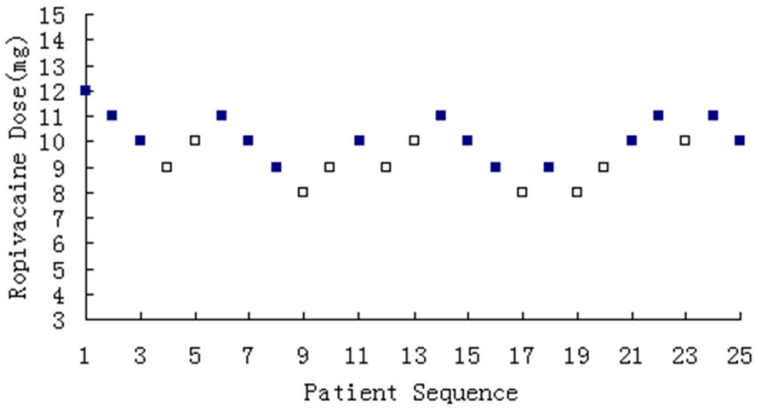

Figure 1. Sequential responses of isobaric ropivacaine with effective (black) or ineffective (white) by up-down method.

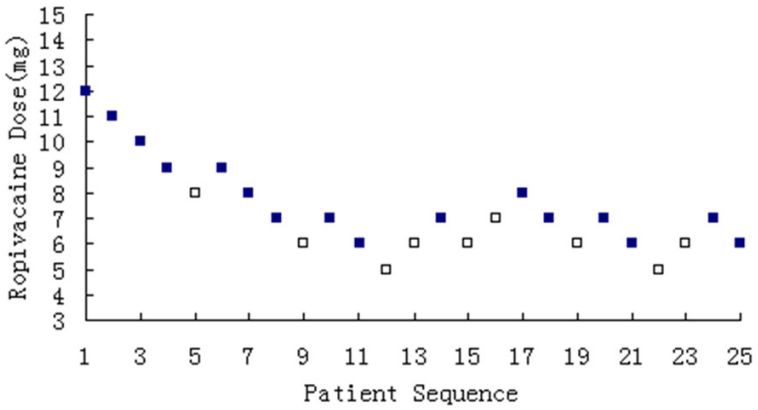

Figure 2. Sequential responses of hyperbaric ropivacaine with effective (black) or ineffective (white) by up-down method.

tion were similar in the two groups (**Table 1**). The results of effective and ineffective spinal anesthesia in two groups are shown in **Figures 1** and **2**. The ED_{50} of isobaric ropivacaine was 9.71 mg (95% CI 8.11-11.32), and the ED_{50} of hyperbaric ropivacaine was 6.55 mg (95% CI 6.07-7.04). The relative potency ratio was 0.67 (95% CI 0.56-0.80) for hyperbaric/isobaric ropivacaine.

Discussion

In this prospective, randomized and double-blind study, we investigated the ED_{50} of intrathecal isobaric and hyperbaric ropivacaine by up-down sequential analysis in the patients undergoing knee arthroscopy, and our results showed the difference in the dose for the requirement of lower extremity surgery between isobaric and hyperbaric ropivacaine. According to our understanding, this is the first study about the direct comparison of potency ratio between isobaric and hyperbaric ropivacaine.

A number of clinical reports have described that intrathecal ropivacaine (isobaric or hyperbaric solutions) is effective and safe for lower limber surgery [1-3]. Several studies showed that in spinal anesthesia, hyperbaric ropivacaine had faster effect onset and more even distribution in cerebrospinal fluid than isobaric ropivacaine [1, 2, 9]. Malinovsky et al [10] evaluated an intrathecal injection of isobaric ropivacaine (15 mg) for urologic endoscopic surgery and found that inadequate spinal anesthesia occurred in 16% of all patients. Fettes et al [11] reported that the patients undergoing elective perineal surgery under spinal anesthesia were randomized to receive isobaric ropivacaine (15 mg) and hyperbaric ropivacaine (15 mg); and nerve blocks were adequate for surgery in all patients receiving hyperbaric ropivacaine, but 17% patients receiving isobaric ropivacaine required general anesthesia because of nerve block failure. Khaw et al [12] compared the effects of spinal anesthesia for elective cesarean delivery between isobaric and hyperbaric ropivacaine, and found that increasing the density of ropivacaine by addition of glucose could change the clinical characteristics of subarachnoid blockade with a higher success rate. All studies above suggest that hyperbaric solutions which act as the diluents of ropivacaine play a main role in spinal anaesthesia. Therefore, further studies are needed to determine whether the ED_{50} dose of hyperbaric solution is lower than that of isobaric solution for achieving similar effective anesthesia. However, so far, little information is available regarding this issue.

The result of our present study showed that the addition of glucose into ropivacaine changed the density of ropivacaine, resulting in different

requirements in the doses between isobaric and hyperbaric ropivacaine for lower extremity surgery. Our study indicated that the potency ratio of hyperbaric ropivacaine was significantly higher than that of isobaric ropivacaine, which is consistent with the results of other studies above. In our present study, the density of isobaric ropivacaine was 0.9998, and the density of hyperbaric ropivacaine 1.0199. According to the average density of cerebrospinal fluid of 1.0003 ± 0.0003, we believe that high density is conducive to the sufficient distribution of ropivacaine in cerebrospinal fluid. Therefore, the distribution of ropivacaine in cerebrospinal fluid is more sufficient in hyperbaric ropivacaine than in isobaric ropivacaine.

However, there were some limitations in our study. First, because our primary aim was to determine the potency ratio of isobaric to hyperbaric ropivacaine, we did not observe the duration of subarachnoid block. Secondly, in this study, the potency ratios of hyperbaric to isobaric ropivacaine was performed at one point of the dose-response curve, and the values for ED_{50} can not be directly translated to actual dose for clinical practice. The pharmacodynamics and pharmacokinetics about ropivacaine of various densities remain to be further investigated.

In summary, the ED_{50} values of hyperbaric ropivacaine and isobaric ropivacaine were 6.55 mg (95% CI 6.07-7.04) and 9.71 mg (95% CI 8.11-11.32), respectively, in knee arthroscopy. The relative potency ratio for hyperbaric/isobaric ropivacaine was 0.67 (95% CI 0.56-0.80). We conclude that the ED_{50} of 0.5% hyperbaric ropivacaine is less than that of 0.5% isobaric ropivacaine in subarachnoid block anesthesia for knee arthroscopy.

Disclosure of conflict of interest

None.

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References

[1] Whiteside JB, Burke D, Wildsmith JA. Comparison of ropivacaine 0.5% (in glucose 5%) with bupivacaine 0.5% (in glucose 8%) for spinal anaesthesia for elective surgery. Br J Anaesth 2003; 90: 304-308.

[2] Kallio H, Snall EV, Tuomas CA, Rosenberg PH. Comparison of hyperbaric and plain ropivacaine 15mg in spinal anaesthesia for limb surgery. Br J Anaesth 2004; 93: 664-669.

[3] Lee YY, Ngan Kee WD, Chang HK, So CL, Gin T. Spinal ropivacaine for lower limb surgery: a dose-response study. Anesth Analg 2007; 105: 520-523.

[4] McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery. Br J Anaesth 2002; 89: 702-706.

[5] Fanelli G, Danelli G, Zasa M, Baciarello M, Di Cianni S, Leone S. Intrathecal ropivacaine 5 mg/ml for outpatient knee arthroscopy: a comparison with lidocaine 10 mg/ml. Acta Anaesthesiol Scand 2009; 53: 109-115.

[6] Camorcia M, Capogna G, Berritta C, Columb MO. The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine. Anesth Analg 2007; 104: 904-107.

[7] Dixon WJ, Massey FJ. Introduction to statistical analysis. 4th edition. New York: McGraw-Hill; 1983. pp. 428-439.

[8] Lee YY, Warwick D, Ngan Kee WD, Fong SY, Liu JT, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. Anesth Analg 2009; 109: 1331-1334.

[9] Chung CJ, Chio SR, Yeo KH, Park HS, Lee SI, Chin YJ. Hyperbaric spinal ropivacaine for cesarean delievery: a comparison to hyperbaric bupivacaine. Anesth Analg 2001; 93: 157-161.

[10] Malinovsky JM, Charles F, Kick O, Lepage JY, Malinge M, Cozian A, Bouchot O, Pinaud M. Intrathecal anesthesia: ropivacaine vs bupivacaine. Anesth Analg 2000; 91: 1457-1460.

[11] Fettes PD, Hocking G, Peterson MK, Luck JF, Wildsmith JA. Comparsion of plain and hyperbaric solutions of ropivacaine for spinal anaesthesia. Br J Anaesth 2005; 94: 107-111.

[12] Khaw KS, Nang Kee WD. Wong M, Ng F, Lee A. Spinal ropivacaine for cesarean delivery: a comparison of hyperbaric and plain solutions. Anesth Analg 2002; 94: 680-685.