Int J Clin Exp Med 2016;9(4):7438-7444
www.ijcem.com /ISSN:1940-5901/IJCEM0011187

Original Article

Combined use of hyperbaric and hypobaric ropivacaine for caesarean section: a prospective, double-blind, randomized, controlled study

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Received June 8, 2015; Accepted August 1, 2015; Epub April 15, 2016; Published April 30, 2016

Abstract: Background: Sequential subarachnoid injection of hyperbaric and hypobaric ropivacaine was evaluated during spinal anesthesia for caesarean section. The effects of different contents of the hyperbaric ropivacaine on the hemodynamic characteristics of the parients were also explored. Methods: The patients meeting inclusion criteria (n=120) were randomly allocated into either the 5 mg hyperbaric ropivacaine + 5 mg hypobaric ropivacaine group (Group A, n=40), 4 mg hyperbaric ropivacaine + 6 mg hypobaric ropivacaine group (Group B, n=40), or 3 mg hyperbaric ropivacaine + 7 mg hypobaric ropivacaine group (Group C, n=40). The primary endpoint was the incidence of hypotension, with secondary endpoints including maximum height of sensory block and the time to reach sensory block to the T8 level. Results: The incidence of hypotension was significantly lower in Group C compared to Group A (8% vs. 45%, P<0.001). The time to reach sensory block to T8 level was 6.4 ± 1.5, 7.5 ± 1.4 and 9.2 ± 2.0 in each group, respectively (P<0.001). Maximum height of sensory block decreased following the reduction of the content of hyperbaric ropivacaine. The median (first quartile-third quartile) [(Q1-Q3)] were T3 (T2.5-T4), T4 (T3-T5), and T6 (T4-T6) in each group, respectively (P<0.001). Group A and Group B had higher incidences of nausea compared to Group C (36% and 25% vs 5%, P<0.001 and P=0.012, respectively). Conclusions: Decreased content of the hyperbaric ropivacaine in the combined group resulted in an increased anesthesia induction time, decreased sensory blockade plane and incidence of hypotension.

Keywords: Spinal anesthesia, hyperbaric ropivacaine, hypobaric ropivacaine, caesarean section

Introduction

Spinal anesthesia is currently utilized in patients undergoing caesarean section [1-4]. However, uncontrollability of the upper plane of anesthesia and higher incidence of hypotension are the main drawbacks during anesthesia, which is caused by greater diffusion of the anesthetic toward the thoracic segments. Spread of anesthetics is influenced by the baricity, dose and the patient position. Therefore, the current study explored the effects of content change of hyperbaric solution in the anesthetic on the regulation of the spread of local anesthetic using a local anesthetic dose and patient position.

In the present study, hyperbaric combined with hypobaric ropivacaine was used for spinal anesthesia in patients undergoing caesarean section. The initial hyperbaric solution spread toward the lowest position of the thoracic segments (T6-7), and the subsequent hypobaric solution moved to the highest position of the lumbar segments (L3). This unique technique, unlike isobaric anesthetics, was not affected by the physical properties of the cerebrospinal fluid [5-9], which could lead to an unpredictability of the level of sensory blockade [10]. This sequential injection of hyperbaric and hypobaric solutions is different from single hyperbaric or hypobaric solutions, which only moves to one side. A previous study by our group (unpublished) showed that equal contents of hyperbaric and hypobaric ropivacaine had significantly lower incidence of hypotension compared with single hyperbaric ropivacaine. Thus, the aim of the present study was to observe the effects of different contents of the combined

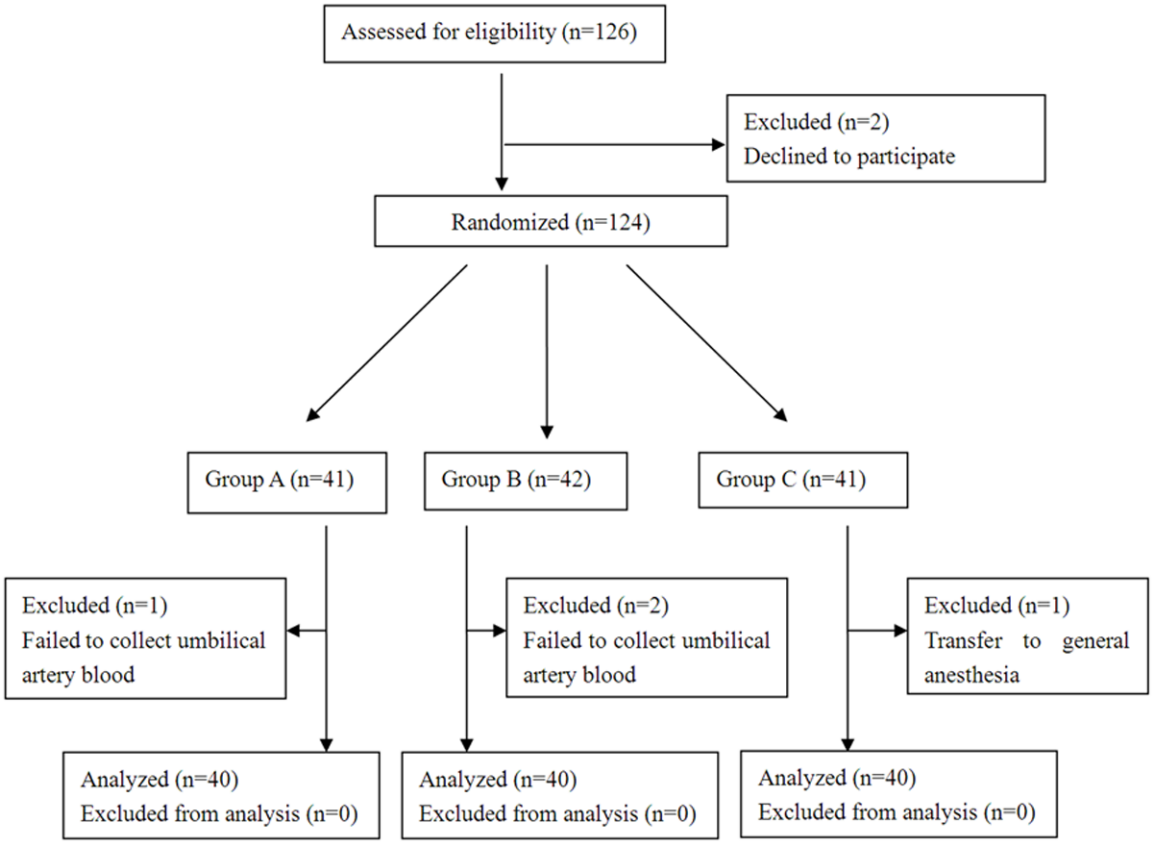

Figure 1. Study flow diagram for the patients undergoing elective caesarean section using a combined spinal-epidural procedure.

solutions on the hemodynamic data of the patient and newborns.

Materials and methods

Study design and subject allocation

This prospective, double-blind, randomized, controlled study was approved by the local medical review committee, and registered in the Chinese Clinical Trial Register (ChiCTR-TRC-13004242). All patients provided written informed consent prior to inclusion.

A total of 120 ASA physical status I or II patients (gestational age ≥37 weeks, singleton) undergoing elective cesarean delivery under combined spinal-epidural anesthesia were included in this randomized, controlled study. Exclusion criteria included age <18 years, height <150 cm or >180 cm, weight <50 kg or >100 kg, hypertension, multiple pregnancy, placenta previa, cardiovascular, cerebrovascular diseases, known abnormal fetal development, or contraindications for intraspinal anesthesia and signs of onset of labor.

All patients were preoperatively fasted for 8 hours and water deprived for more than 4 hours. The patients were maintained in a supine position with a 15° left lateral tilt after entering the operation room. Each patient was rapidly administered 7 mL/kg of 6% hydroxyethyl starch (200/0.5) within 10 min via a 16-gauge cannula placed in the forearm veins. The infusion speed was then adjusted to 7 mL/kg•h. Blood pressure was monitored 1 min following infusion, and the mean value of three consecutive detections was recorded.

Patients were randomly allocated into three groups (A, B and C) using a computer-generated table. An investigator who was responsible for the random allocation and preparation of spinal anesthetics was not present during surgery and postoperative evaluations. The anesthetics used in all the three groups consisted of 10 mg 0.5% ropivacaine and 10 μg 0.005% fentanyl in 2 mL solution (The total volume of all solutions in each group was equal, and the hyperbaric and hypobaric ropivacaine solutions were sequentially injected into the subarach-

Table 1. Baseline characteristics of all patients meeting the inclusion criteria

	Group A (n=40)	Group B (n=40)	Group C (n=40)	*P* value
Age (yr)	28 (21-42)	30 (18-45)	27 (20-41)	0.405
Height (cm)	162 (152-173)	163 (147-172)	160 (154-175)	0.107
Weight (kg)	73 (51-93)	75 (52-89)	72 (58-87)	0.312
Gestational age (wk)	38 (37-39)	38 (37-40)	38 (37-40)	0.405
Volume of intraoperative transfusion (mL)	901 ± 70	883 ± 68	871 ± 78	0.180
Volume of intraoperative urine (mL)	166 ± 54	177 ± 46	170 ± 52	0.630
Volume of blood loss (mL)	413 ± 51	396 ± 91	432 ± 71	0.096
Catheter insertion time (min)	1.7 (1-4)	1.8 (1-3)	1.8 (1-3)	0.871
Operation time (min)	39 (27-48)	41 (29-50)	38 (29-51)	0.194
Complete analgesia time (min)	139 ± 14	132 ± 16	139 ± 15	0.203
Baseline				
Systolic AP (mmHg)	134 ± 16	131 ± 13	129 ± 11	0.387
Diastolic AP (mmHg)	61 ± 9	62 ± 10	64 ± 10	0.470
Mean AP (mmHg)	86 ± 8	87 ± 7	87 ± 7	0.401
HR (beats/min)	85 ± 11	84 ± 11	83 ± 10	0.959

Values presented as mean ± SD or median (min-max).

Table 2. Neonatal characteristics

	Group A (n=40)	Group B (n=40)	Group C (n=40)	*P* value
Birth weight (g)	3215 ± 485	3310 ± 557	3212 ± 474	0.328
Apgar at 1 min	9 (7-10)	9 (8-9)	9 (8-10)	0.293
Apgar at 5 min	10 (8-10)	10 (9-10)	10 (9-10)	0.385
pH (UA)	7.25 ± 0.06	7.26 ± 0.05	7.27 ± 0.06[a]	0.130
pH (UV)	7.33 ± 0.05	7.34 ± 0.08	7.36 ± 0.03	0.184

Values presented as mean ± SD or median (min-max). [a]*P*=0.045 vs. Group A.

noid space rather than injected together), which are shown as follows:

Group A: Syringe A1: 5 mg hyperbaric ropivacaine and 5 μg fentanyl (1 mL); Syringe A2: 5 mg hypobaric ropivacaine and 5 μg fentanyl (1 mL); Group B: Syringe B1: 4 mg hyperbaric ropivacaine and 4 μg fentanyl (0.8 mL); Syringe B2: 6 mg hypobaric ropivacaine and 6 μg fentanyl (1.2 mL); Group C: Syringe C1: 3 mg hyperbaric ropivacaine and 3 μg fentanyl (0.6 mL); Syringe C2: 7 mg hypobaric ropivacaine and 7 μg fentanyl (1.4 mL).

Ten percent glucose and sterile distilled water were used to prepare the hyperbaric and hypobaric ropivacaine, respectively. All patients received hyperbaric (Syringe 1) and hypobaric (Syringe 2) solutions sequentially after the subarachnoid puncture. The interval of administrations for syringes 1 and 2 was 3-5 s.

A combined spinal-epidural procedure was performed at the L2-3 interspace with the patient maintained in the right lateral decubitus position (25 G, 17 G Whitacre, Weiss, Becton Drive, USA). Anesthetics in syringes 1 and 2 were both injected upwards (towards the shadowless lamp) when the needle entered the subarachnoid space. Injection speed in the three groups was 0.1 mL/s. The spinal anesthesia needle was withdrawn and 3 cm of the epidural catheter was placed into the epidural space. Immediately after the epidural catheter was taped into place, the patients in the two groups were turned to the supine position with a left lateral tilt of 15°. All preoperative and postoperative assessments were made by independent anesthetists blinded to the anesthetic technique. The level of sensory block to sharp pinprick was assessed with a 24-gauge blunted needle bilaterally along the mid-clavicular line at 1-min intervals for 20 min. If the T6 sensory blockade level was not achieved, an epidural supplement of 2% lidocaine was administered to maintain a T6 sensory level. Hypotension was defined as systolic arterial pressure (AP) <90 mmHg or a decrease in systolic AP >20% from baseline. When perioperative systolic AP decreased to this level, 6 mg ephedrine was administered every 2 min until the systolic AP was maintained within normal range. Atropine (0.3 mg) was used to treat bradycardia (heart rate <50/min).

Table 3. Hemodynamic data and blockade characteristics of the patients

	Group A (n=40)	Group B (n=40)	Group C (n=40)	*P* value
Incidence of hypotension (%)	18 (45%)	11 (28%)	3 (8%)[a]	0.001
Total dose of ephedrine (mg)	0 (0-24)	0 (0-18)	0 (0-12)[b,c]	<0.001
Time to reach sensory block to T8 level (min)	6.4 ± 1.5	7.5 ± 1.4[d]	9.2 ± 2.0[e,f]	<0.001

Values presented as n (%) or median (min-max) or mean ± SD. [a]*P*<0.001 vs. Group A; [b]*P*<0.001 vs. Group A; [c]*P*=0.017 vs. Group B; [d]*P*=0.005 vs. Group A; [e]*P*<0.001 vs. Group A; [f]*P*<0.001 vs. Group B.

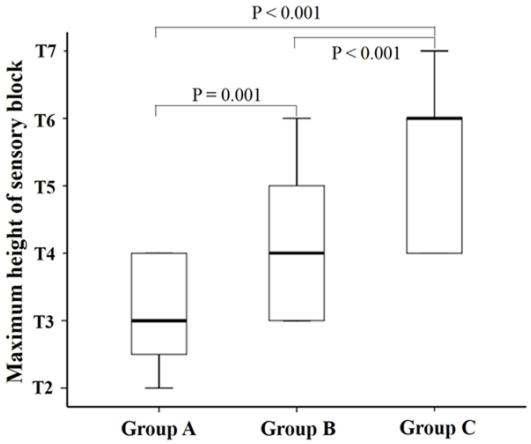

Figure 2. Maximum height of sensory block decreased following the reduction of the content of hyperbaric ropivacaine. The heavy line represents median sensory block height, the box represents the interquartile range, and the error bars represent max and min values. The median (Q1-Q3) were T3 (T2.5-T4), T4 (T3-T5), and T6 (T4-T6) in each group, respectively (P=0.001 for Group A vs. Group B; P<0.001 for Group A vs. Group C and Group B vs. Group C).

Hemodynamic data, maximum height of blockade level, time to reach sensory block to T8 level, volume of intraoperative transfusion, volume of intraoperative urine, volume of intraoperative blood loss, insertion time of the epidural catheter, operation time, complete analgesia time [beginning of intrathecal injection to a visual analogue scale (VAS) >0], total dose of ephedrine and incidence of complications (including nausea, vomiting, shivering, dizziness and sleepiness) were recorded. Neonatal conditions were assessed using Apgar scores at 1 and 5 min, and blood gas analyses of the umbilical artery and vein were also performed.

Statistical analyses

Primary outcome was the incidence of hypotension. Secondary outcomes were maximum height of sensory block and the time to reach sensory block to T8 level. Using a pilot study, 40 patients per group were required for 90% power to detect a significant difference of 35% in the incidence of hypotension between the groups at the P<0.05 significance level.

SPSS 17.0 software was used for statistical analyses. Data were analyzed using the Shapiro-Wilks test to determine distribution. If normally distributed, the data were presented as mean ± SD and groups were compared using one-way ANOVA. The LSD method was used for multiple comparisons. Data distributed non-normally were presented as median (min-max) or (first quartile-third quartile) [(Q1-Q3)] and analyzed using a Kruskal-Wallis H test. Categorical variables were analyzed using a chi-square test, or Fisher's exact test if the number of subjects in any contingency table cell was expected to be less than five. P<0.05 was considered statistically significant. Partitions of chi-square method was used in a multiple comparison of three groups and P<0.0125 was considered statistically significant.

Results

In total, 126 patients were assessed for study eligibility; two refused to participate, and 124 patients were randomized with 41 in Group A, 42 in Group B and 41 in Group C. Four patients did not meet inclusion criteria, among which one in Group A and two in Group B failed to collect the umbilical artery blood, and one in Group C transferred to general anesthesia due to intraoperative massive hemorrhage. Ultimately, there were 40 patients analyzed in each group (**Figure 1**).

Baseline characteristics of the patients including insertion time of the epidural catheter, operation time, volume of intraoperative transfusion, urine and blood loss, and blood pressure were not statistically different between groups (**Table 1**). Supplemental anesthetics were administered into the epidural space of four patients perioperatively in Group C. Operative condition evaluation and complete analgesia

Table 4. Incidence of patient complications

	Group A (n=40)	Group B (n=40)	Group C (n=40)	*P* value
Nausea	15 (36%)	10 (25%)	2 (5%)[a,b]	0.002
Vomiting	9 (22%)	4 (10%)	0 (0%)[c]	0.005
Shivering	21 (53%)	24 (60%)	18 (45%)	0.406
Dizziness	4 (10%)	1 (3%)	0 (0%)	0.066
Sleepiness	0 (0%)	0 (0%)	1 (3%)	0.365

Values presented as n (%). [a]*P*<0.001 vs. Group A; [b]*P*=0.012 vs. Group B; [c]*P*=0.002 vs. Group A.

time were not statistically different between groups (**Table 1**).

Neonatal characteristics including birth weight, Apgar scores at 1 and 5 min were also comparable in three groups. The pH value of UA in Group C was significantly higher compared with that in Group A (7.27 ± 0.06 vs. 7.25 ± 0.06, P=0.045, **Table 2**).

Hemodynamic data from intrathecal injection to delivery of the shoulder suggested that the incidences of hypotension were 45%, 28% and 8% (P=0.001) in each group, respectively. A statistical difference was found between Group A and Group C (P<0.001). The total dose of ephedrine was significantly lower in Group C [0 (0-12)] compared with Group A [0 (0-24)] or Group B [0 (0-18)] (P<0.001, P=0.017, respectively). The time to reach sensory block to T8 level was 6.4 ± 1.5, 7.5 ± 1.4 and 9.2 ± 2.0 in each group, respectively (P<0.001). Significant differences were found between Group A and Group B (*P*=0.005), Group A and Group C (P<0.001) and Group B and Group C (P<0.001) (**Table 3**).

Maximum height of sensory block decreased following the reduction of the content of hyperbaric ropivacaine. The median (Q1-Q3) were T3 (T2.5-T4), T4 (T3-T5), and T6 (T4-T6) in each group, respectively (P<0.001) (**Figure 2**).

Group A and Group B had higher incidences of nausea compared to Group C (36% and 25% vs 5%, P<0.001 and P=0.012, respectively). The incidence of vomiting in Group C was significantly lower than in Group A (0 vs. 22%, P=0.002). No patient in either group had residual neurological symptoms during follow-ups (**Table 4**).

Discussion

The present study showed that a longer time was required to reach sensory block to T8 level following a decreased proportion of hyperbaric solution. In addition, maximum height of blockade level also gradually reduced, and there was a trend of decrease of the incidences in hypotension and nausea. The reasons for these results could be reduced spread of the anesthetics toward T6-7 due to decreased proportion of hyperbaric ropivacaine in the mixed solution, which reduced the maximum height of blockade level and the incidence of hypotension. Therefore, incidences of nausea in parturient and acidemia in newborns were decreased. Supplemental anesthetics were administered into the epidural space of four patients in Group C because the anesthesia plane did not reach T6. Previous reports showed that a height of spinal anesthesia including T4-T8 could be chosen for caesarean section, and a recent study [11] indicated that T6 was an optimal height of spinal anesthesia for cesarean section.

In this study, hyperbaric and hypobaric solutions were administered successively into the intrathecal space through the L2-3 interspace. Hyperbaric solutions will redistribute because of gravity and move to the lowest point of the thoracic curve, situated around T6-7 in pregnant women, and the second half dose of the hypobaric solution rose to L3. These two successively administered solutions with different baricities did not flow to one side as the single baricity solution. This unique technique helped ropivacaine to uniformly spread cephalad and caudally. Although it is uncertain whether the sequential subarachnoid injection of the anesthetics with different baricities would separate excellently, our data showed an obvious trend that change of the content of hyperbaric solution could regulate the maximum height of blockade level.

Spinal anesthesia is the optimal choice for elective caesarean section [12]. The advantages of spinal anesthesia include rapid onset of analgesia and continuous spreading. However, these properties may cause hypotension during caesarean section [3, 13-15]. Several reports demonstrated a relationship between a lower dose of anesthetic and incidence of hypotension [16, 17]. In addition, anesthesia provid-

ers can control the spread of the blockade by choice of patient positioning, which could also decrease the incidence of hypotension. However, this method requires the patient to receive spinal anesthesia in a sitting position for 5 min before turning to the supine position [18, 19]. The technique of combined use of hyperbaric and hypobaric ropivacaine could be performed in the lateral decubitus position and was unnecessary to deliberately maintain a certain position. On the other hand, this combined technique is more suitable for combined spinal-epidural anesthesia. Unilateral spinal anesthesia would not be caused if cannulation of the epidural catheter is difficult after spinal anesthesia in the lateral decubitus position [11]. This unique technique has several advantages including isobaric anesthetics, but unlike isobaric anesthetics, would not be affected by the physical properties of the cerebrospinal fluid [5-9], which could lead to an unpredictability of the level of sensory blockade [10]. The combined technique also keeps the advantage of hyperbaric anesthetics that the anesthesia provider can adjust the level of sensory blockade by patient positioning.

Cesur et al [20] compared the effects of sequential administration of plain and hyperbaric ropivacaine with the single hyperbaric ropivacaine. The results showed that there were no statistical differences of maximum height of blockade level and time to reach sensory block to T6 between two groups, however, a significantly decreased incidence of hypotension was found in the combined group. In the present study, combined use of hyperbaric and hypobaric anesthetics resulting in a reduced incidence of hypotension following a decreased content of the hyperbaric anesthetic. The change of the content of hyperbaric anesthetic also influenced the maximum height of blockade level and time to reach sensory block to T8. The reason could be a less spread of the hyperbaric anesthetic to T6 compared with the plain anesthetic, which indicates that sequential administration of anesthetic with different baricities will not change the property of spread of each content, and the anesthetics moves in the cerebrospinal fluid according to their baricities. Furthermore, decreasing the content of hyperbaric ropivacaine resulted in an increased anesthesia induction time. Particularly, the time to reach sensory blockade to T8 in Group C was about 9 min. This prolonged anesthesia induction is inappropriate for emergent cesarean section.

The limitation of this unique technique includes the anesthetics with different baricities should be separately loaded in different syringes, which results in a loss of the local anesthetics while exchanging the syringes. However, this missing dose is negligible through the observation. One advantage of this combined procedure is to regulate the anesthesia induction time and maximum height of blockade level via changing the content of the hyperbaric ropivacaine.

In addition, we are interested in another possible advantage of this combined procedure, which include alleviating the tendency of anesthesia plane inclining to one side caused by longer time of epidural catheter when patients receive combined spinal-epidural anesthesia in a lateral decubitus position because the sequential administration of hyperbaric and hypobaric ropivacaine moving to both sides of the spinal nerve root. Thus, this method should have the advantage similar to isobaric anesthetic and avoid spreading only to one side such as an anesthetic with single baricity.

Other possible effects of this method include mitigating adverse effects caused by misjudgment of the interspace of lumbar vertebrae (L2-3 or L3-4) because combined procedure reduces the dependence on lumbar vertebral interval compared to the solution with single baricity.

Conclusion

Maximum height of blockade level could be regulated via changing the content of the hyperbaric ropivacaine in the combined procedure in spinal anesthesia. Decreased blockade level results in a steady hemodynamic characteristics and is beneficial to the newborns.

Acknowledgements

Beijing Youan Hospital Capital Medical University, 2016 young talent incubation project (NYKT20160020).

Disclosure of conflict of interest

None.

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