Original Article

A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia

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Abstract

Background: Recently introduced ropivacaine is 40% less potent than bupivacaine. Ropivacaine made hyperbaric by the addition of dextrose is known to provide reliable spinal anesthesia (SA).This study was designed to compare the clinical efficacy of equal doses of hyperbaric 0.5% ropivacaine with 0.5% bupivacaine for SA.

Materials and Methods: Eighty American Society of Anesthesiologists grade I-II patients undergoing elective infraumbilical surgeries under SA were recruited and randomized to receive 3ml of hyperbaric ropivacaine 5mg/ml containing dextrose 83 mg/ml (by the addition of desired dose of 25% dextrose) in Group R or 3ml of hyperbaric bupivacaine 5mg/ml containing dextrose 80 mg/ml in Group B. Monitoring of vitals and observation for the block parameters were carried out. The data were presented as mean with a standard deviation and frequency with percentage. Statistical analysis was performed using InStat computer software with appropriate tests and $P < 0.05$ was considered to be significant.

Results: Ropivacaine produced a slower onset of sensory block (ropivacaine 4.5 min; bupivacaine 3.2 min; $P < 0.05$) and the mean total duration of sensory block was significantly lesser (ropivacaine155 min; bupivacaine 190.5 min; $P < 0.05$). Patients in the ropivacaine Group R had significantly more rapid recovery from the motor blockade (ropivacaine120 min; bupivacaine 190 min; $P < 0.05$) and passed urine sooner than the patients in bupivacaine Group B (ropivacaine 257 min; bupivacaine 358 min; $P < 0.05$).

Conclusion: Ropivacaine 15 mg in dextrose 8.3% provides reliable SA of shorter duration than bupivacaine 15 mg in 8% dextrose.

Key words: Hyperbaric bupivacaine, ropivacaine, spinal anesthesia

Introduction

Ropivacaine, a newer amino-amide local anesthetic (LA) agent similar to bupivacaine in chemical structure, but 30-40% less potent than bupivacaine has been well-studied for spinal anesthesia (SA).[1-4] The preliminary studies evaluated the efficacy and safety of isobaric ropivacaine for neuraxial blockade.[5,6] Intrathecal ropivacaine was found to be safe, having shorter duration of action than bupivacaine and lesser incidence of transient neurological symptoms (TNS) as compared with intrathecal lignocaine.[7,8] Intrathecal use of hyperbaric LA agents have become more popular as they produce predictable block characteristics and reliable SA.[3,4] Presently only isobaric preparations of ropivacaine are commercially available for the reason of difficulty in maintaining the pharmacological stability of hyperbaric solutions for clinical use. Thus, the aim of this study was to compare the clinical efficacy of 0.5% ropivacaine (made hyperbaric by the addition of desired dose of dextrose from autoclaved 10 ml ampoule of 25% dextrose) with commercial hyperbaric 0.5% bupivacaine using equal doses (15 mg) of almost similar specific gravities and to assess the suitability of ropivacaine as an alternative to lignocaine for intermediate duration of surgeries under SA.

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.130031

Materials and Methods

A pilot study was conducted on 10 patients receiving intrathecal 3 ml of hyperbaric 0.5% ropivacaine (83 mg/ml dextrose). Autoclaved ampoules of 25%, 10 ml dextrose

were used for each patient to maintain sterility for mixing with commercially available sterile isobaric ropivacaine for intrathecal use. Samples of hyperbaric 0.5% ropivacaine (containing dextrose 83 mg/ml) were sent to the laboratory to test the specific gravity and for culture sensitivity. Another ten patients received intrathecal 3 ml of commercial hyperbaric 0.5% bupivacaine, and these samples were also tested for specific gravity in the same laboratory. The mean specific gravity of hyperbaric ropivacaine and bupivacaine noted. All patients were observed for block parameters, hemodynamic changes and for complications following SA. Following a pilot study, eighty patients gave written informed consent for the prospective double blind study, which was approved by the local research ethical committee. Patients of American Society of Anesthesiologists (ASA) grade I-II undergoing lower-abdominal, perineal or lower-limb surgery under SA were enrolled for the study. Eighty sealed envelopes labeled inside for Group R (n = 40) and Group B (n = 40) were mixed together. Patients who met the inclusion criteria were randomized in double blind fashion by picking up the sealed envelope to receive 3 ml of ropivacaine 5 mg/ml (with dextrose 83 mg/ml) in Group R or 3 ml of hyperbaric bupivacaine 5 mg/ml (containing dextrose 80 mg/ml) in Group B [Table 1]. For anxiolysis oral diazepam, 5-10 mg at night before surgery was given. On arrival in the anesthetic room, continuous monitoring with electrocardiogram, non-invasive arterial blood pressure and pulse oximetry were started. Intravenous (IV) infusion was given with 8 ml/kg of ringer lactate over 20 min before SA. Pre-medication in the form of (IV) glycopyrrolate 0.004 mg/kg, midazolam 0.05 mg/kg and anti-aspiration prophylaxis with 10 mg metoclopramide and 50 mg ranitidine IV was given. Patients were placed in the left lateral position for lumbar puncture, and SA was performed using a midline approach at the L3-4 or L4-5 intervertebral space. A 25-Guage Quincke needle (Becton Dickinson S.A, Madrid, Spain) was inserted with the distal port facing laterally and the appropriate LA drug was injected over 10-15s. The hyperbaric ropivacaine solution was prepared aseptically (by an anesthetist who was not one of the investigators), immediately before injection by adding 1 ml (250 mg) of autoclaved 25% dextrose ampule (10 ml) to 2 ml of commercially available sterile preservative free isobaric solution of 0.75% ropivacaine (Ropin Neon). The bupivacaine 0.5% solution used was commercially available in India (Anawin Heavy, Neon). Patients were placed supine immediately after injection. The development of the block was recorded by an investigator who was blind to the nature and type of solution injected. The extent of sensory block (analgesia to pinprick), degree of lower limb motor block(with James modified Bromage Scale as used by Fettes *et al.*,[3]: 0 = full movement; 1 = inability to raise extended leg, can bend knee; 2 = inability to bend knee, can flex ankle; 3 = no movement), arterial blood pressure and heart rate were recorded at 2 min interval for first 10 min post-injection and at 5 min intervals thereafter until two consecutive levels of sensory block were identical to consider it as fixation of the level, after which assessment was performed every 15 min interval until regression to T10 and then at 30 min intervals thereafter until complete regression of the sensory level at S2 and motor blockade of grade 0 on bromage scale was observed. Hypotension, defined as a decrease in systolic pressure >30% from baseline, was treated with IV bolus of 5ml/kg ringers lactate and if needed phenylephrine 50 mcg. Fluids were administered to replace intraoperative losses. Bladder catheterization was performed only if surgically indicated. After surgery, patients were encouraged to mobilize under supervision only when the sensory block had regressed beyond L1 and the time of first micturition was noted. All patients were visited at 24 h and telephoned twice in a week later to identify any adverse sequelae.

Table 1: Study groups

Groups	Intrathecal hyperbaric LA drugused
Group R (n=40)	3 ml of ropivacaine 5 mg/ml (with glucose 83 mg/ml)
Group B (n=40)	3 ml of hyperbaric bupivacaine 5 mg/ml (containing glucose 80 mg/ml)

LA = Local anesthetic

Statistical analysis

To evaluate the block characteristics with intrathecal hyperbaric ropivacaine and bupivacaine duration of sensory block observed during a pilot study was considered to select the sample size. On simple interactive statistical analysis, sample size of minimum 28 was derived using the formula for sample size calculation for multiple comparison (two tailed) based on the assumption of α (type 1 error) = 5%, β (type 2 error) = 0.2 and power of the study = 80% to detect a difference of 35%. To increase the power of study, we included 40 patients in each group. Data were analyzed using InStat computer software. Numerical variables were presented as mean and standard deviation for patient characteristics such as age, weight, height, hemodynamic changes, block parameters such as onset, duration and recovery time of sensory block, time to maximum motor blockade, duration of motor blockade and the time to first micturition. Categorical variables were presented as frequency and percent for patients' characteristics such as sex distribution, ASA status and type of surgery, bromage grade of motor blockade and incidence of adverse events such as hypotension, bradycardia, backache, post-dural puncture headache (PDPH), TNS and for the need of general anesthesia (GA) supplementation. Student's "Unpaired *t*-test" for comparisons of mean and proportion

were used wherever appropriate. $P < 0.05$ was considered to be statistically significant.

Results

In the pilot study,the mean specific gravity of the hyperbaric 0.5% ropivacaine solution (by the addition of 83mg/ml dextrose) observed was 1.0300 (0.0015) and the samples were negative for bacterial culture. The mean specific gravity of hyperbaric bupivacaine (Anawin Heavy, Neon) was reported to be 1.0250 (0.0001). In this double-blind prospective study, groups were comparable with regard to age, sex, height, weight; ASA status and type of surgery, [Table 2]. Observations about the block characteristics are mentioned in Table 3. The onset of pinprick analgesia at T10 was more rapid in bupivacaine Group B than in ropivacaine Group R ($P = 0.034$, $P < 0.05$). However, the time to (peak) maximum extent of cephalad spread and the level achieved were similar in both groups. The mean duration of sensory block was shorter in Group R than in Group B ($P = 0.028$, $P < 0.05$). The maximum block height achieved was T6 (T4-9) and T5 (T3-8) respectively in Group R and Group B, ($P > 0.05$). The time to maximum motor blockade was statistically similar ($P = 0.10$, $P > 0.05$) and the duration of motor blockade was greater in Group B than in Group R. The mean time to complete regression of motor blockade was 190 ± 35 min with intrathecal bupivacaine (Group B) as compared to 120 ± 20 min with hyperbaric ropivacaine (Group R) ($P = 0.00$, $P < 0.05$). The degree of motor blockade was significantly greater in Group B patients than in group R patients. Motor blockade of bromage grade III was observed in 36 (90%) and 28 (70%) of the patients in Group B and R respectively ($P = 0.03$, $P < 0.05$). Grade II bromage scale observed in 10 (25%) and 4 (10%) in Group R and B respectively ($P = 0.08$, $P > 0.05$). All patients underwent surgery under SA successfully. Two patients had less motor blockade of bromage grade I in Group R (who underwent perineal surgery and amputation of toes of diabetic foot) and no other patient in both groups required supplementation with GA. Hemodynamic changes were insignificant when compared between the two groups ($P > 0.05$). Table 4 mentions the frequency of adverse events.

In bupivacaine group 11 (27.5%) patients, in ropivacaine group 8 (20%) patients required phenylephrine for hypotension ($P > 0.05$). No significant difference in the incidence of bradycardia was observed in two groups and they responded easily to injection atropine. Four patients in Group R and six patients in Group B developed mild, localized, self-limiting tenderness at the site of lumbar puncture at 24 h, but there were no neurological symptoms in any patient. Two patients in each group developed a mild PDPH, treated with bed rest, fluids and analgesic. Patients in the ropivacaine group were able to pass urine sooner than those in the bupivacaine group ($P < 0.05$).

Table 2: Patient characteristics and types of surgery

Demographic profile and type of surgeries	Group R ropivacaine (n = 40)	Group B bupivacaine (n = 40)
Female/male	19/21	23/17
ASA status (I/II)	32/8	30/10
Age (year)	36.47±11.16	38.55±13.95
Weight (kg)	59.12±7.43	58.87±8.32
Height (cm)	158.62±8.61	162.07±7.52
Type of surgery		
Lower limb	15	13
Perineal	6	8
Inguinal	5	6
Lower abdomen	14	13

Data are expressed as mean (SD) or frequencies, ASA = American society of anesthesiologists

Table 3: Characteristics of subarachnoid block (SAB)

Observations of SAB	Group R (n = 40)	Group B (n = 40)	t and P value with significance
Onset time of sensory block (min)	4.3 (3.5)	3.2 (1.5)	t=2.159, P=0.0339, S
Time to peak sensory block (min)	13.5 (6)	15 (3)	t=1.41, P=0.16, S
Duration of sensory block (min)	155 (60)	190.5 (80)	t=2.245, P=0.0276, S
Time to complete motor blockade (min)	14.5 (9)	11 (10)	t=1.645, P=0.1039, NS
Duration of motor blockade (min)	120 (20)	190 (35)	t=10.98, P=0, S
Bromage grade 3 (n, %)	28 (70)	36 (90)	t=2.236, P=0.028, S
Bromage grade 2 (n, %)	10 (25)	4 (10)	t=1.765, P=0.0814, NS
Bromage grade 1 (n, %)	2 (5)	0	S
Bromage grade 0 (n, %)	0	0	NS

NS = Not significant ($P > 0.05$), S = Significant ($P < 0.05$)

Discussion

Early studies with isobaric ropivacaine reported to have variable or inadequate block patterns foe surgery[5,6] and confirmed that the addition of glucose to the solution of ropivacaine has better effects as with other drugs used for SA.[3,4] It reduces the proportion of a limited block or more extensive block which has

Table 4: The frequency of adverse events

Adverseevents, *n* (%)	Group R ropivacaine (*n* = 40)	Group B bupivacaine (*n* = 40)	*t* and *P* value
Hypotension	8 (20)	11 (27.5)	t=0.79, P=0.43 NS, P>0.05
Bradycardia	3 (7.5)	4 (10)	t=0.39, P=0.69 NS, P>0.05
GA supplementation	0	0	t=0, P=1.00 NS, P>0.05
Backache	4 (10)	6 (15)	t=0.68, P=0.49 NS, P>0.05
Post-dural puncture headache	2 (5)	2 (5)	t=0, P=1.00 NS, P>0.05
Transient neurological symptoms	0	0	t=0, P=1.00 NS, P>0.05
Time to first micturition (min)	257.27±43.75	358.12±46.93	t=9.94, P=0.000 S, P<0.05

NS = Not significant (P > 0.05), S = Significant (P < 0.05). GA = General anesthesia

been previously reported from studies on both tetracaine[9] and bupivacaine.[10-13] As hyperbaric ropivacaine is not available commercially, addition of glucose 3-10% to ropivacaine has been used and studied for surgeries under SA.[1-4,9,10,14-16] In our study, the concentration of dextrose (83 mg/ml, 8.3%) used is similar to that of commercially available hyperbaric bupivacaine (80 mg/ml, 8%). We used readily available 25% 10 ml dextrose ampoules, autoclaved to prevent the risk of bacterial contamination. It is known that ropivacaine is 30-40% less potent and effects are short lived than bupivacaine making it advantageous for short to intermediate duration of surgeries or ambulatory surgeries.[14,17] We observed that ropivacaine significantly produced slower onset but shorter time to peak effect (4.5 min, 13.5 min) than bupivacaine (3.2 min, 15 min); however, the level of sensory block achieved was similar and the duration of sensory block was significantly lesser with ropivacaine. The findings were similar to the study carried out in elective surgeries under SA by Whiteside and others[2] who observed onset time of 5 and 2 min with 3 ml of 0.5% hyperbaric ropivacaine and bupivacaine in 5% and 8% glucose respectively.

We observed that ropivacaine has a less potent effect on motor nerves and the degree of sensory-motor separation is more as compared with bupivacaine, but can produce reliable SA, which has been supported by similar observations of other studies.[18,19] The findings were similar to the study carried out by Whiteside and others,[2] who observed mean onset time of motor blockade of 15 min and 10 min and total duration of around 90 min and 180 min with similar dose of hyperbaric ropivacaine and bupivacaine respectively. Luck *et al*.[15] Also observed less degree and duration of motor blockade, lower incidence of bromage score of grade III in 63% with hyperbaric 0.5% ropivacaine as compared to 90% with 0.5% bupivacaine, with the similar dose of 3 ml with 30 mg/ml of glucose. We also observed grade III bromage score in 70% and 90% of patients receiving intrathecal hyperbaric ropivacaine and bupivacaine respectively. Lee *et al*. studied intrathecal isobaric ropivacaine in different concentrations (2, 4, 7, 10 and 14 mg) for lower limb surgeries and found 100% successful anesthesia with the dose of 14 mg of ropivacaine.[20] We also noted that compared to bupivacaine ropivacaine group had good sensory blocks, favorable recovery profile of sensory/motor blockade and shorter time to first micturition. These features of ropivacaine are beneficial for ambulatory surgery. Hyperbaric lignocaine 5% has been used as a short-acting agent for ambulatory SA, but currently its use is restricted due to a high incidence of TNS.[8,21] We found no evidence of any late sequelae such as backache or other transient symptoms in this study as with previous studies of ropivacaine.[1-4] Hence, ropivacaine can be a safer alternative for ambulatory surgeries.

It is now, well-established that physical properties such as specific gravity, density and baricity of drug related to cerebrospinal fluid (CSF) determines the intrathecal spread of the drug, compared with plain solutions. Khaw *et al.* compared plain and hyperbaric ropivacaine for cesarean delivery in a dose of 25 mg with or without glucose 8.3% intrathecally. They observed faster onset and recovery, extensive spread and greater success rates with hyperbaric ropivacaine. They observed specific gravity of plain ropivacaine 1.0092 and that of hyperbaric ropivacaine to be 1.0345 at 37°C.[16] We observed mean specific gravity of hyperbaric 0.5% ropivacaine (with 8.3% dextrose) to be1.0300 at 27°C, which is comparable to the specific gravity of 1.0250 with that of commercial heavy bupivacaine 0.5% (with 8% glucose) when tested in our laboratory. Schiffer et al. studied the influence of CSF density on the extent of plain bupivacaine for spinal anesthesia and has shown that with a higher CSF density, a higher spinal block level could be expected.[22] Wille reviewed various studies on isobaric and hyperbaric ropivacaine compared with bupivacaine. He concluded that intrathecal administration of isobaric ropivacaine is supported with evidence for the safe use of hyperbaric ropivacaine by the addition of 3-8% glucose for surgeries under SA including cesarean section and day care surgeries.[23]

There are few limitations with our study, due to non-availability of standard densitometer, exact density or baricity of hyperbaric ropivacaine was not estimated and hence, only specific gravity was tested during a pilot study. The specific gravities/densities

of hyperbaric solutions mentioned in the literature and the mean specific gravity of both the hyperbaric preparations observed in our study were comparable. Besides, hyperbaric ropivacaine is not available commercially; extreme antiseptic care is required to prepare the hyperbaric solution. Hence, use of autoclaved dextrose ampoule was preferred and can be used safely to avoid the risk of contamination.

Conclusion

This study shows that 0.5% ropivacaine (in 8.3% dextrose), made hyperbaric relative to CSF, can be easily prepared. It is comparable to the readily available hyperbaric 0.5% bupivacaine (in 8% glucose) in terms of quality of block, but with a shorter recovery profile making it a useful agent for SA for intermediate duration of surgeries.

Acknowledgment

We acknowledge the support of our D. Y. Patil Institution for publishing this work.

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How to cite this article: Kulkarni KR, Deshpande S, Namazi I, Singh SK, Kondilya K. A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia. J Anaesthesiol Clin Pharmacol 2014;30:238-42.
Source of Support: Nil, **Conflict of Interest:** None declared.