Isobaric forms of ropivacaine *vs.* bupivacaine in lower abdominal surgeries: a hospital-based, prospective, comparative study

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Abstract

We aimed to assess whether ropivacaine (0.75%; 22.5 mg) can replace bupivacaine (0.5%; 15 mg) as a better intrathecal anesthetic in lower abdominal surgery. In this hospital-based, single-blind, randomized, prospective, comparative study, 100 patients of either sex, aged between 18 and 70 years, weighing 40–80 kg, with American Society of Anesthesiologists physical status 1 and 2, and undergoing lower abdominal surgery were randomly allocated into two groups to receive intrathecal isobaric bupivacaine 0.5% 3 mL (15 mg) or ropivacaine 0.75% 3 mL (22.5 mg). In the intraoperative period, the onset, efficacy, duration, and regression of sensory and motor blockade and the quality of anesthesia and hemodynamic effects were observed at regular intervals. The ropivacaine and bupivacaine groups were comparable for demographic parameters. The duration of onset of sensory and motor blocks was significantly shorter in the bupivacaine group ($P < 0.01$). In the ropivacaine group, a faster recovery from sensory block ($P = 0.02$) and higher segmental height [thoracic (T)10 and T8] were achieved ($P < 0.01$). Bradycardia and hypotension were insignificant in the ropivacaine group ($P > 0.05$). Isobaric ropivacaine is a better spinal anesthetic in lower abdominal surgeries as it provides faster recovery from sensory block and a higher level of segmental sensory block with fewer side-effects.

Key words: bupivacaine; hemodynamic effects; intrathecal anesthetic; isobaric forms; lower abdominal surgery; motor block; ropivacaine; segmental height; sensory block; spinal anesthesia

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Introduction

Bupivacaine is one of the first few drugs approved for spinal anesthesia.[1] It exhibits a long duration of action and dense sensory and motor action.[2] However, side-effects of bupivacaine, such as bradycardia, hypotension, motor paralysis, and cardiac and central nervous system toxicity, have also been reported, which have led to the search for alternatives with better properties such as short and rapid action with minimal side-effects.[3-7]

One of the recent alternatives to bupivacaine is ropivacaine, its isomer (more specifically, its propyl analogue), which is a long-acting amide with less lipid solubility and toxicity. This low lipid solubility causes less motor block[8] as it blocks A-alpha and C fibers, thereby carrying information related to muscle sense more slowly than bupivacaine does.[9] Ropivacaine, however, has a shorter duration of action, with less intense and faster recovery of motor blockade, enabling earlier postoperative mobilization.[10] Further, ropivacaine and bupivacaine are available in isobaric and hyperbaric forms. In an isobaric form, the intrathecal spread of the anesthetic is not affected by the position of the patient during and after injection.[10,11]

Comparative studies of intrathecal, isobaric ropivacaine and bupivacaine are limited.[12] The present study focused on determining the potential of 0.75% ropivacaine in replacing 0.5% bupivacaine as a long-acting, intrathecal anesthetic for patients undergoing lower abdominal surgery. The primary objective of the study was to compare the efficacy of isobaric ropivacaine versus bupivacaine, using the duration of the recovery of sensory and motor block. Further, the segmental height of sensory block was evaluated as the secondary objective.

Subjects and Methods

Study design

This hospital-based, single-blind, randomized, prospective, comparative study was carried out in a tertiary care hospital over a period of 2 years (2012–2014) after getting approval from the Institutional Ethics Committee on September 14, 2009 (**Additional file 1**). This study follows the CONsolidated Standards Of Reporting Trials (CONSORT) statement (**Additional file 2**).

Selection criteria & grouping

A total of 100 patients of either sex aged 18–70 years, weighing 40–80 kg, with American Society of Anesthesiologists physical status I and II, and scheduled to undergo elective lower abdominal and lower limb surgery under intrathecal anesthesia in our tertiary care hospital, were considered for the study, after we obtained their written informed consent (**Additional file 3**). Patients with gross spinal deformity, local infection, neurological diseases, bleeding disorder, cardio-respiratory diseases, or liver diseases; chronic users of narcotics, sedatives, or alcohol; and those allergic to any of the medications used in the study were excluded from the study.

All the patients were equally divided and randomly allocated

with the help of computer-generated random numbers and sequentially numbered envelops, in a single-blind (patient) manner to a bupivacaine group (**Figure 1**): receiving intrathecal isobaric bupivacaine (0.5%, 3 mL, 15 mg; Buloc P, Celon Laboratories, Hyderabad, India), and a ropivacaine group: receiving intrathecal isobaric ropivacaine (0.75%, 3 mL, 22.5 mg; Ropizuva Abbott, Navsari, Gujarat, India), with 50 patients in each group.

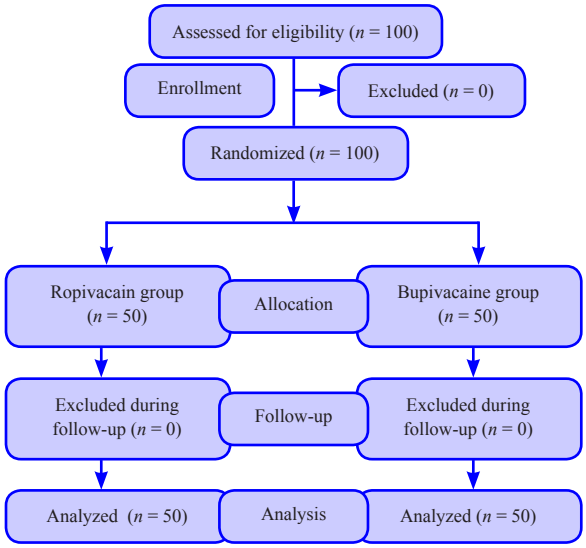

Figure 1: Study flow chart.

Study procedure

A day before the surgery, each patient was administered a diazepam tablet (10 mg, Sun Pharma, Vadodara, Gujarat, India) orally for anxiolysis. The anesthesiologist performed subarachnoid block under aseptic conditions using a 25-gauge Quincke needle (0.5 mm) by a midline lumbar puncture at the L3–4 interspace in the lateral recumbent position. After free flow of clear cerebrospinal fluid was assured, the anesthetic drug (either isobaric bupivacaine or isobaric ropivacaine) was injected slowly to respective group members in a supine position. The time of intrathecal injection was considered as 0, and parameters such as sensory block (onset, level, and duration of recovery), motor block (onset, block regression, and duration of recovery), vitals (heart ratio and breath pressure), and side-effects (hypotension, bradycardia, and respiratory depression) were recorded.

Sensory block was assessed by loss of sensation to pinprick using a 23-G sterile needle. The onset or induction of sensory block was the time from intrathecal injection administration to the loss of the pinprick sensation at the L2 segment. The assessment was initiated just after the administration of the agent and continued every 15 seconds, till the loss of pinprick sensation at the L2 level. After 30 minutes of subarachnoid blockage and at the end of surgery, the dermatome (area of skin with a single spinal nerve) level of sensory block was noted (maximum level of sensory block). This was followed by assessment at 15-minute intervals, till the return of the pinprick sensation to the L2 dermatome was reported.

Motor block assessment was initiated immediately after intrathecal injection by using the modified Bromage scale (grade 0: no paralysis; grade 1: unable to raise extended legs but can flex knees; grade 2: unable to flex knees but can flex ankle; grade 3: unable to flex ankle, complete motor block).[13] The onset of motor block was taken as the time to achieve Bromage score 3 from the time of subarachnoid blockage injection. Thereafter, motor block regression was noted, and the duration for complete motor block recovery was taken as the time from subarachnoid injection to the return of the Bromage score to zero.

Vitals were recorded every 5 minutes throughout the intraoperative period and at the completion of surgery. Hypotension was managed with ephedrine (6 mg; Alergin, Cipla, India) injection in increments; bradycardia was managed with intravenous atropine (Atrisolon, Intas, India) injection at 0.01 mg/kg. After complete resolution of motor blockade, the patients were shifted to the postoperative ward or recovery ward.

Statistical analysis

For effect size (Cohen's $\delta = 0.6$, medium), the significance level, power, and sample size in each group were 95%, 80%, and ~45, respectively, for the independent sample *t*-test.

The data were expressed as mean ± standard deviation. Mann-Whitney *U* test, independent two-sample *t*-test, and chi-square test were performed using R software (https://www.r-project.org). Data were considered statistically significant when $P < 0.05$.

Results

Demographic and continuous variables of study patients under isobaric bupivacaine or isobaric ropivacaine anesthesia

All 100 patients completed this prospective study. The demographic parameters of patients, including age, sex, body mass, and height, were comparable between the groups ($P > 0.05$). Mean age, body mass, and height in the ropivacaine group were 41.3 ± 10.28 years, 62.78 ± 10.22 kg, and 163.9 ± 10.23 cm, and for the bupivacaine group, 39.04 ± 11.04 years, 62.6 ± 10.14 kg, and 163.52 ± 9.76 cm, respectively (**Table 1**). The type of surgery and their numbers were appendicectomy ($n = 10$), below knee amputation ($n = 2$), femoral plating ($n = 1$), inguinal hernioplasty ($n = 23$), and tibia plating ($n = 14$).

Onset and level of sensory and motor block under isobaric bupivacaine or isobaric ropivacaine anesthesia

In the comparison of the average time taken for the onset of pain–temperature sensory block ($P = 0.00$) and for the onset of motor block ($P = 0.00$) between the two groups, a significant difference was observed, with the bupivacaine group taking less time than that of the ropivacaine group. In case of average time taken for the onset of touch–pressure sensory block, no significant difference was observed among the two groups ($P = 0.11$; **Table 2**).

The segmental height attained by sensory block after 30 minutes in both groups showed a significant difference [pain–temperature ($P = 0.00$); touch–pressure ($P = 0.00$)] at the T8 and T5 level attained by the majority in the bupivacaine group and at the T10 and T8 level attained by the majority in

Table 1: Comparison of demographic and continuous variables of lower abdominal surgery patients under isobaric bupivacaine or isobaric ropivacaine anesthesia

Variables	Bupivacaine group	Ropivacaine group	*P*-value
Age (yr)			
20–30	12 (24)	9 (18)	0.57
31–40	17 (34)	15 (30)	
41–50	10 (20)	16 (32)	
51–60	11 (22)	10 (20)	
Sex			
Female	11 (22)	13 (26)	0.81
Male	39 (78)	37 (74)	
Body mass (kg)			
41–50	6 (12)	8 (16)	0.91
51–60	15 (30)	13 (26)	
61–70	18 (36)	17 (34)	
71–80	11 (22)	12 (24)	
Height (cm)			
<150	4 (8)	5 (10)	0.47
151–160	14 (28)	12 (24)	
161–170	20 (40)	19 (38)	
171–180	10 (20)	12 (24)	
>180	2 (4)	2 (4)	

Note: Data are expressed as number (percentage) and were analyzed by the chi-square test.

Table 2: Comparison of onset of sensory and motor block of lower abdominal surgery patients under isobaric bupivacaine or isobaric ropivacaine anesthesia

Variables	Bupivacaine group	Ropivacaine group	*P*-value
Pain–temperature (s)[a]	138.2 ± 32.8	158.7 ± 42.6	<0.01
Touch–pressure (min)[a]	4.52 ± 1.28	5.02 ± 1.60	0.11
Motor block (min)[a]	7.76 ± 1.17	8.91 ± 1.31	<0.01
Side-effect[b]			
Bradycardia	6	2	
Hypotension	6	4	

Note: [a]Data are expressed as mean ± SD (n = 50) and were analyzed by the Mann–Whitney U test. [b]Data are expressed as numbers.

the ropivacaine group (**Table 3**). This demonstrates that the ropivacaine group attained a greater height of sensory block than the bupivacaine group.

Further, the two groups were compared for the occurrence of side-effects. No significant difference was observed between the two groups with respect to the incidence of bradycardia and hypotension ($P > 0.05$; **Table 2**).

Recovery from sensory and motor block under isobaric bupivacaine or isobaric ropivacaine anesthesia

During the comparison of the average time taken for recovery from sensory block, a significant difference was observed among the two groups, with mean time taken for complete recovery from pain–temperature ($P = 0.02$) and touch–pressure ($P = 0.00$) sensory block more in the bupivacaine group than in the ropivacaine group (**Table 4**).

Table 3: Comparison of the level of sensory block in 30 minutes of lower abdominal surgery patients under isobaric bupivacaine or isobaric ropivacaine anesthesia

Segmental height of sensory block	Bupivacaine group	Ropivacaine group	*P*-value
Pain–temperature			
T2	0	5 (10)	<0.01
T6	6 (12)	3 (6)	
T7	15 (30)	0	
T8	20 (40)	4 (8)	
T10	6 (12)	32 (64)	
T12	3 (6)	6 (12)	
Touch–pressure			
T4	11 (22)	3 (6)	<0.01
T5	16 (32)	2 (4)	
T6	14 (28)	5 (10)	
T7	2 (4)	4 (8)	
T8	6 (12)	26 (52)	
T9	1 (2)	0	
T10	0	4 (4)	

Note: Data are expressed as number (percentage) and were analyzed by the chi-square test.

Table 4: Comparison of the duration of recovery (min) from sensory and motor block of lower abdominal surgery patients under isobaric bupivacaine or isobaric ropivacaine anesthesia

Variables	Bupivacaine group	Ropivacaine group	*P*-value
Sensory block			
Pain–temperature	176.0 ± 16.3	159.0 ± 19.3	0.02
Touch–pressure	160.0 ± 15.9	140.0 ± 15.7	<0.01
Motor block	187.0 ± 17.3	182.0 ± 15.3	0.93

Note: Data are expressed as mean ± SD (n = 50) and were analyzed by the independent two-sample t-test.

In contrast, while comparing the mean time taken for complete recovery from motor block, no significant difference was observed between the two groups ($P = 0.93$; **Table 4**).

Discussion

The present study focused on determining the potential of 0.75% ropivacaine in replacing 0.5% bupivacaine as a long-acting intrathecal anesthetic for patients undergoing lower abdominal surgery. The primary objective of the study was to evaluate the efficacy of isobaric ropivacaine with bupivacaine, using the duration of recovery of sensory and motor block. Further, the segmental height of the sensory block was evaluated as the secondary objective. Consequently, a more effective, safer, less toxic drug with an early recovery profile is still being investigated to improve the safety issues.[14] In our prospective study, the results demonstrate rapid segmental (thoracic) sensory block (T10 for pain–temperature and T8 for touch–pressure) with 0.75% isobaric ropivacaine as compared to 0.5% isobaric bupivacaine.

Ropivacaine and bupivacaine are highly lipid soluble, with isobaric and hyperbaric forms exhibiting sodium chan-

nel inhibition. In isobaric form, the intrathecal spread of the anesthetic is not affected by the position of the patient during and after injection.[10,11] The administration of 15 mg of isobaric bupivacaine compared with 22.5 mg of isobaric ropivacaine provided more rapid sensory and motor block, as the time taken by bupivacaine was less, even at a lower dose than that of ropivacaine. This is in accordance with a study in which the patients received 10 mg of isobaric bupivacaine and 15 mg of isobaric ropivacaine for spinal anesthesia. The bupivacaine group took less time for the onset of sensory block, indicating its better effectiveness even at a low dosage.[15] As the time of sensory block caused by bupivacaine is lower than that of ropivacaine, our results argue for a difference of approximately 12.6% in the time of onset of the block, which could be due to a difference in their pharmacokinetics.

Segmental height achieved by sensory block was more in the ropivacaine group than in the bupivacaine group, as the highest level of sensory block achieved by ropivacaine was at T10 and T8. This is comparable to a recent study performed by Verma et al.[12] which showed that the highest level of sensory block achieved by ropivacaine was also at T10. This stipulates that the spread of ropivacaine is much faster than that of bupivacaine, which could be due to the use of a high dosage of ropivacaine.[12] In contrast, a study conducted by Boztuğ et al.[16] showed that the segmental height achieved by bupivacaine was at T11 and that by ropivacaine was T8, indicating faster spread by bupivacaine even at a lower dosage, which makes our findings arguable and open for future research.

In our study, the recovery from sensory blockade was assessed at the level of T10. Ropivacaine was less predictable in the height of anesthesia and not as efficient in achieving adequate analgesia. The mean full recovery from sensory blockade at T10 in the ropivacaine group was significantly shorter than in the bupivacaine group. These findings are analogous to those in other studies, which concluded faster subsidence of sensory blockade with ropivacaine than with bupivacaine.[14,17] However, a study conducted by Kallio et al.[18] yielded contrasting findings, as the time of recovery for sensory block was significantly longer with ropivacaine than with bupivacaine. This could be due to the less lipophilic nature of ropivacaine, causing shallower penetration into large myelinated motor fibers and resulting in a relatively fast recovery.

In the present prospective study, intrathecal ropivacaine provided a high degree of cardiovascular stability, with low incidence of bradycardia and hypotension as compared to bupivacaine, although no significant difference was observed. A similar finding was observed in a recent study, which showed no visible difference, but 4.4% patients received ephedrine for hypotension, and 6.6% patients received atropine for bradycardia in the bupivacaine group.[19] As compared to bupivacaine, ropivacaine has lower potential for central nervous system and cardiac toxic effects.[20]

Commercially, ropivacaine is available in isobaric form. Hence, the present study compared it with isobaric bupivacaine. Consequently, this study lacked a comparative evaluation of hyperbaric ropivacaine with isobaric bupivacaine, which is known to impart better quality and spread of motor and sensory block.[21] This could be a potential limitation of our study.

Although no major side-effects were noticed in our study, further studies are warranted to rule out any long-term or short-term adverse effects of the drugs. Besides, the study involved only patients undergoing lower abdominal surgeries. Going forward, future studies need to be conducted using smaller doses of both the intrathecal agents to assess whether similar results can be achieved with lower doses and fewer complications.

The current study findings demonstrate a higher level of segmental sensory block, shorter duration of recovery from sensory block, and lower rate of side-effects and complications with 22.5 mg of 0.75% ropivacaine as compared to 15 mg of 0.5% bupivacaine. The study findings indicate that isobaric ropivacaine could be used as a replacement for isobaric bupivacaine in lower abdominal surgeries.

Author contributions

Study implementation: PP and VKD; data analysis: PVD. All authors were involved in the concept and design, and manuscript preparation, read and approved the final manuscript.

Conflicts of interest

The authors have no conflict of interest to declare.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Additional files

Additional file 1: Hospital ethics approval.
Additional file 2: CONSORT checklist.
Additional file 3: Informed consent form.

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CONSORT Checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1-2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2-3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2-3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment		Dates defining the periods of recruitment and follow-up	NA
		Why the trial ended or was stopped	NA
Baseline data	14	A table showing baseline demographic and clinical characteristics for each group	5
Numbers analysed	15	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	16a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5,6,7
	16b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	17	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	18	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	19	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7,8,9
Generalisability	20	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	21	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7,8,9,