Comparative evaluation of intrathecal administration of newer local anaesthetic agents Ropivacaine and Levobupivacaine with Bupivacaine in patients undergoing lower limb surgery

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Citation

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Abstract

This study aimed to detect if intrathecal (i.t.) ropivacaine and levobupivacaine provided anaesthesia (satisfactory analgesia and muscular relaxation) and postoperative analgesia of similar quality to bupivacaine in patients undergoing lower limb surgeries. 75 patients were enrolled. Patients were randomly assigned to receive one of the following isobaric intrathecal (i.t.) solutions: bupivacaine 15 mg (n=25), levobupivacaine 15 mg (n=25), or ropivacaine 15 mg (n=25). An i.t. solution was considered effective if an upper sensory level to pinprick of T6 or above was achieved and if intraoperative supplementation was not required. Sensory, motor and hemodynamic changes were recorded. Anaesthesia was effective in 100, 96, and 96% of patients in the bupivacaine 15 mg, levobupivacaine 15 mg, and ropivacaine 15 mg groups, respectively. Bupivacaine and levobupivacaine 15 mg were associated with a significantly superior success rate to that observed in the ropivacaine group ($P<0.05$). They also provided a longer duration of analgesia and motor block ($P<0.05$) vs levobupivacaine and ropivacaine). The levobupivacaine and ropivacaine are an interesting alternative to racemic bupivacaine.

INTRODUCTION

Over the past few years, the use of bupivacaine for outpatient spinal anesthesia has increased because of reports stating the potential neurotoxicity of spinal lidocaine ([1]). Intrathecal bupivacaine has low (1%) incidence of post operative complications ([2]), but Bupivacaine has been shown to have selective cardiac effects more pronounced with R-isomer than S-isomer. Long-acting local anesthetics induce marked negative inotropic and lusitropic effects. Among LAAs, levobupivacaine exerts the greater depressant effects but Ropivacaine is less cardio toxic on a mg basis than bupivacaine ([3]). Ropivacaine and Levobupivacaine are alternative long-acting local anaesthetic with significant central nervous system ([4], [5]) toxicity thus seem to be an attractive alternatives to bupivacaine.

The findings for both ropivacaine and levobupivacaine in comparison to bupivacaine when given intrathecal are inconsistent in various studies concluding that the advantages were not clinically significant when single shot spinal anesthesia ([6],[7]) was considered. In some studies no significant differences were found between the onset of motor and sensory block in patients who received ropivacaine and bupivacaine intrathecal ([8]), whereas in others ropivacaine was shown to have a longer onset of block ([9]). Because of their close chemical relationship, levobupivacaine and racemic bupivacaine share many pharmacokinetic properties, but studies have found the sensory blockade lasted significantly longer with levobupivacaine than with racemic bupivacaine ([10]).

The lack of comparative studies, controversies and inadequate information on the anesthetic potency and efficacy of intrathecally administered isobaric ropivacaine and levobupivacaine in comparison to racemic bupivacaine, we performed this randomized, double-blinded crossover study to address two issues, to evaluate the anaesthetic safety and efficacy of these newer anaesthetic drugs in lower limb surgeries.

MATERIAL & METHODS

After obtaining informed consent and approval from the local ethics committee the present study will be conducted in the Deptt. Of Anaesthesiology and Intensive care, Govt. Medical College, Jammu.

The study included 75 patients scheduled for hip or lower limb surgeries, ASA grade-I and grade-II, age 18-80 yrs, weight 60-110kg and height above 160 cm. Exclusion criteria were known hypersensitivity to amide local anesthetics and general contraindications against spinal anesthesia.

The patients were randomly assigned according to according to a computer-generated table of randomization into 3 (three) groups. Group A (n=25): received intrathecal 15 mg of isobaric bupivacaine. Group B (n=25): received intrathecal 15 mg of isobaric ropivacaine. Group C (n=25): received intrathecal 15 mg of isobaric levobupivacaine. The random assignments were prepared outside the study center and delivered in sealed, opaque, sequentially numbered. Baseline values of pulse, noninvasive blood pressure and respiratory rate will be recorded. Basic demographic characteristics like age, sex, weight and height were noted.

The patients were kept fasting overnight and received tablet Alprazolam 0.25mg orally the night before and with sip of water two hrs before operation. Premedication and I.V line with 18G I.V. cannula was established. Each patient was preloaded with 10ml/kg infusion of Ringer Lactate 1hr before surgery. Monitored variables included continuous electrocardiogram (lead II), heart rate, arterial blood pressure (by noninvasive means), and pulse oximetry (SpO2) and base line vitals noted. The patient was placed in the lateral position. Under all aseptic precautions and after local infiltration of the skin with 1% lidocaine, the subarachnoid space was entered at the L3-4 interspace via the midline approach using a 25 G Quincke's spinal needle. Correct needle placement will be identified by free flow of cerebrospinal fluid and study drug injected at the rate of 0.2ml/s. The spinal needle was removed and the patient placed supine to carry out the initial assessments. Throughout the procedure the patients received oxygen 3 l/min through ventimask along with continuous noninvasive monitoring.

Onset of sensory block assessed in the normal limb by assessing the changes in pin prick sensation every 1min till no sensation (grade 2) is achieved (graded according to Gromley and Hill 1996, {Normal sensation - 0, Blunted sensation -1, No sensation -2}) Grade 2 was taken as onset of sensory block.

Onset of Motor block assessed every 1 min till complete motor block is achieved (grade 3) in the normal limb. (Graded according Modified Bromage scale {0 = no paralysis, able to flex hips/knees/ankles; 1 = able to move knees, unable to raise extended legs; 2 = able to flex ankles, unable to flex knees; 3 = unable to move any part of the lower limb}). Grade 3 was taken as complete motor block.

Intraoperative monitoring of pain; was assessed with the help of a Linear Visual analogue scale using a ten cm line where 0 is denotes “no pain” and 10 denotes “worst possible pain” every 15 min after onset of surgery till the end of surgery.

Duration of sensory block; was taken as the time from the onset of sensory block to the time when the patient requires first dose of analgesia for post operative pain.

Duration of motor block (recovery of motor blockade to grade 1); was taken as the time from complete motor block to when the patient recovers the ability to flex knees i.e. grade 1 on Bromage scale.

Quality of block was graded as Adequate - no sedation/analgesia required, Inadequate - need of additional analgesia, Failed - GA required. If the level of analgesia was inadequate, the regimen was switched to general anesthesia and excluded from the study.

Intraoperative noninvasive monitoring of vitals (HR, SBP, DBP and SPO2) was done every 1 min for first 5 min, every 2 min for next 15 min and 5 min thereafter till the completion of surgical procedure.

Side effects like Hypotension (will be categorized as either fall in SBP to less than 100mm Hg or decrease in MBP of more than 20% from baseline), Bradycardia (a heart rate <50 bpm was defined as bradycardia and treated with 0.5 mg of atropine), Nausea/Vomiting, Headache and Backache were documented.

RESULTS

Demographic data and the mean duration of surgery are compiled in Table 1. One patient in the Levobupivacaine and ropivacaine group required supplemental anesthesia during skin incision because of a failed block for technical reasons

and was not evaluated further. All statistical analyses were therefore based on 24 patients in the Levobupivacaine and ropivacaine group and 25 patients in the Bupivacaine group.

Figure 1

Table 1: Demographical distribution of patients

Groups → Variables↓		Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Age (in years) →	Mean ± SD	43.44±	42.52±	40.56±
	Range	19-75	19-75	18-75
Weight (in Kg's) →	Mean ± SD	60.36±6.43	59.76±6.49	59.56±7.98
	Range	43-70	45-70	42-70
Height (in Cm's) →	Mean ± SD	172.24±9.69	173.36±8.68	170±7.61
	Range	150-190	162-190	160-184
Sex	Males	16	17	18
	Females	9	8	7
Duration of surgery (in minutes)	Mean ± SD	94.4±	95.3±	100.8±
	Range	45-160	50-180	50-160
Quality of block	Adequate	25	24	24
	Inadequate /failed		1	1

Mean onset of sensory block (in min) was comparable in group A (Isobaric Bupivacaine) and group C (Isobaric Levobupivacaine) but longer group B (Isobaric Ropivacaine) with statistically intergroup differences.(Table 2)

Figure 2

Table 2: Onset of sensory block (in min)

	Stats.	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Onset of sensory block (in min)	Mean ± SD	4.40 ± 1.81	5.45 ± 1.00	4.38 ± 1.53
	Intergroup comparison Bonferroni's 't' test	A vs B 0.014	A vs C 0.876	B vs C 0.013

The *P-value* = 0.016 (**significant**)
F(2,72) 4.39

Mean onset of motor block (in min) was comparable in group A (Isobaric Bupivacaine) and group C (Isobaric Levobupivacaine) but longer group B (Isobaric Ropivacaine) with statistically intergroup differences.(Table 3)

Figure 3

Table 3: Onset of Motor block (in min)

	Stats.	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Onset of sensory block (in min)	Mean ± SD	5.67 ± 1.94	6.46 ± 1.14	5.46 ± 1.72
	Intergroup comparison Bonferroni's 't' test	A vs B 0.001	A vs C 0.570	B vs C 0.017

The *P-value* = 0.050 (**significant**)
F(2,72) 5.75

The maximum value of visual analogue scale during the operation per patient was taken as the value of intra operative visual analogue scale. Mean Intraoperative Visual Analogue Score (VAS) in group A (Isobaric Bupivacaine) was 0.68 ± 0,. group B (Isobaric Ropivacaine) was 0.52 ± 0.09 and in group C (Isobaric Levobupivacaine) was 0.52 ± 0.091. (Table 4)

Figure 4

Table 4: Intraoperative Visual Analogue Score (VAS)

	Stats.	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Intraoperative visual analogue scale	Mean ± SD	0.68 ± 0.12	0.52 ± 0.09	0.52 ± 0.091
	Range	0-7	0-8	0-8

The *P-value* = 0.91 (**not significant**)
F(2,72) 0.084

Mean duration of sensory block (in min) was comparable in group A (Isobaric Bupivacaine) and group C (Isobaric Levobupivacaine) but longer group B (Isobaric Ropivacaine) with statistically intergroup differences (Table 5)

Figure 5

Table 5: Duration of sensory block (in min)

	Stats.	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Onset of sensory block (in min)	Mean ± SD	175.76 ± 50.0	144.32 ± 32.1	189.4 ± 42.9
	Intergroup comparison Bonferroni's 't' test	A vs B 0.14	A vs C 0.34	B vs C 0.001

The *P-value* = 0.008 (**significant**)
F(2,72) 7.74

Mean duration of motor block (in min) was comparable in group A (Isobaric Bupivacaine) and group C (Isobaric

Levobupivacaine) but longer group B (Isobaric Ropivacaine) with statistically intergroup differences (Table 6)

Figure 6

Table 6: Duration of Motor block (in min)

	Stats.	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Onset of sensory block (in min)	Mean ± SD	169.8 ± 47.6	128.24 ± 29.1	172.76 ± 38.9
	Intergroup comparison Bonferroni's 't' test	A vs B 0.01	A vs C 0.34	B vs C 0.001

The *P-value* = 0.001 (**significant**)
F(2,72) 8.01

There was a slight decrease in mean heart rates and arterial blood pressures over 30 min after anesthesia which however was not associated with significant intergroup differences in hemodynamics. SpO2 remained stable throughout the observation period. None of the patients with sufficient spinal anesthesia required supplemental oxygen. Hemodynamic and respiratory variables remained stable from skin incision throughout the surgical procedure. No patient required blood replacement.

Total number of patients who had hypotension in group A (Isobaric Bupivacaine) was 2 .Only 2 patients had failed block and was given General Anaesthesia for surgery to be performed. (Table 7)

Figure 7

Table 7: Side Effects

Group → Side effects ↓	Group A Isobaric Bupivacaine	Group B Isobaric Ropivacaine	Group C Isobaric Levobupivacaine
Hypotension	2(8%)	2(8%)	2(8%)
Bradycardia	2(8%)	1(4%)	1(4%)
Nausea / vomiting	2(8%)	2(8%)	2(8%)
Headache	1(4%)	1(4%)	1(4%)
Backache	0	1(4%)	0

DISCUSSION

In our study all the three groups were comparable in Age, Sex, Weight, Height and mean duration of (in min). Onset time and duration of the sensory and motor blocks and hemodynamics are comparable to those obtained with racemic bupivacaine.

In our study with 15 mg of ropivacaine we had inadequate blockade in only one patient i.e. 4% of patients which may be attributed to faulty technique. The dose of 15 mg of intrathecal ropivacaine was associated with 5% inadequate analgesia in lower limb surgeries ([11]). Another study ([9]) reported that intrathecal ropivacaine produced excellent intraoperative analgesia and abdominal muscle relaxation, indistinguishable from spinal bupivacaine.

Our results show that the onset of block was significantly shorter for bupivacaine and levobupivacaine as compared to ropivacaine, which is comparable with certain studies conducted ([12]) in patients undergoing elective surgery concluded that the onset of analgesia as more rapid with bupivacaine. The lesser lipid solubility of ropivacaine may cause this drug to penetrate the large myelinated A fibers more slowly than the more lipid-soluble bupivacaine ([13]). But studies ([8], [14]) which compared the effect of intrathecal plain ropivacaine 5 mg ml–1 with bupivacaine 5 mg ml–1 for major orthopaedic surgery found no difference in the onset of block. Intergroup differences between levobupivacaine and bupivacaine were insignificant in our study which is comparable with another study ([15])

The maximum value of visual analogue scale during the operation per patient in our study are in accordance with studies ([16]) conducted which compared the effects of intrathecal bupivacaine with ropivacaine and found both the drugs having an adequate Intraoperative analgesia.

The study revealed that the duration of block was similar in bupivacaine and levobupivacaine. Although the duration of analgesia was statistically insignificant between bupivacaine and levobupivacaine the mean duration was longer for levobupivacaine. Studies have ([10]) found the blockade lasted significantly longer with levobupivacaine than with racemic bupivacaine which might be attributable to a greater intrinsic vasoconstrictor property of levobupivacaine ([17]). Also it has been shown that ampoules of levobupivacaine contain 7.5 mg ml–1 free base (26.0 mmol litre–1) whereas corresponding ampoules of bupivacaine contain 6.66 mg ml–1 free base (23.1 mmol litre–1) and ampoules of ropivacaine 6.63 mg ml–1 (24.1 mmol litre–1) ([18]).

The duration of block was shorter for ropivacaine as compared to bupivacaine and levobupivacaine in our study. These results confirm that spinal ropivacaine is less potent than bupivacaine and levobupivacaine ([23]). It has been reported that ropivacaine produces vasoconstriction in contrast to vasodilation produced by bupivacaine ([22]). This result was in accordance with another study ([19]) which

suggested that the anesthetic potency ratio between spinal ropivacaine and bupivacaine was of 2:3, with lower anesthetic potency achieved by 15 mg of spinal ropivacaine than by 10 mg of bupivacaine in patients undergoing endoscopic urological surgery. Ropivacaine has been shown to be effective in providing intrathecal anaesthesia for patients undergoing total hip replacement, ($_{21}$), and lower abdominal ($_{11}$) or limb surgery ($_{12}$).

Although levobupivacaine has very similar pharmacokinetic properties to those of racemic bupivacaine, several studies support the notion that its faster protein-binding rate reflects a decreased degree of toxicity. The decreased cardiovascular and central nervous system toxicity makes Ropivacaine and levobupivacaine interesting alternative to racemic bupivacaine in procedures requiring large doses of local anaesthetic but this might not be true in spinal anaesthesia where the dosage of drug is comparatively small.

Conclusion: It can be concluded from the above study that the newer local anaesthetic agent Levobupivacaine has very similar pharmacokinetic properties to those of racemic bupivacaine. Thus it can be used with equal efficacy and better safety as bupivacaine in similar doses in subarachnoid block. The results of this study show that ropivacaine produces adequate spinal blockade of shorter duration with early ambulation and faster home discharge as compared with levobupivacaine and bupivacaine. Thus it can be used intrathecally with equal efficacy and better safety as bupivacaine in similar doses for short surgical procedures

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