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Levobupivacaine or ropivacaine: A randomised double blind controlled trial using equipotent doses in spinal anaesthesia☆,☆☆

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ABSTRACT

Introduction: Levobupivacaine and ropivacaine are relatively new local anaesthetics developed in order to address the issue of bupivacaine toxicity. Although certain differences do exist between their pharmacological profiles, its clinical relevance at equipotent doses is not evident so far.

Objective: To compare the efficacy and characteristics of equipotent doses of intrathecal levobupivacaine with ropivacaine.

Methodology: Sixty ASA grade I/II patients of 18–60 years, either sex posted for lower limb orthopaedic surgery under spinal anaesthesia were randomly given either 15 mg levobupivacaine or 22.5 mg ropivacaine. Sensory and motor block, haemodynamic characteristics, as well as any side effects, were recorded.

Results: Onset of sensory block to T_{10} was more rapid in group R than group L, $p < 0.0001$. The median (range) height achieved in group R was T7 (T5–T10) while in group L was T7 (T4–T10). Time to reach maximum height and time to modified Bromage grade 3 was shorter in group R as compared to group L, $p < 0.0001$. Levobupivacaine produced significantly longer (290.50 ± 34.67) duration of motor block compared to ropivacaine (222.50 ± 23.00). Duration of analgesia was significantly longer in group L (309.83 ± 36.45) than group R (249.50 ± 22.83). No serious adverse effects were recorded.

Conclusion: Levobupivacaine produces significantly longer duration of analgesia than ropivacaine when used in a ratio of 0.6:1. Efficacy, toxicity and haemodynamic profile make ropivacaine suitable agent for surgeries with low threshold for hypotension.

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Levobupivacaína o ropivacaína: un ensayo aleatorio doble ciego controlado con dosis equipotentes en la anestesia espinal

Palabras clave:
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RESUMEN

Introducción: La levobupivacaína y la ropivacaína son anestésicos locales relativamente nuevos, desarrollados con el fin de abordar la cuestión de la toxicidad de la bupivacaína. Aunque existen ciertas diferencias entre sus perfiles farmacológicos, su relevancia clínica en dosis equipotentes no es evidente hasta ahora.

Objetivo: Comparar la eficacia y las características de las dosis equipotentes de levobupivacaína por vía intratecal con las de ropivacaína.

Metodología: A Sesenta pacientes de grado ASA I/II de 18 a 60 años y de ambos sexos, programados para cirugía ortopédica del miembro inferior bajo anestesia espinal, se les dio al azar o bien 15 mg de levobupivacaína o 22,5 mg de ropivacaína. El bloqueo motor, el bloqueo sensorial, las características hemodinámicas y cualquier otro efecto secundario fueron registrados.

Resultados: El inicio del bloqueo sensorial en T10 fue más rápido en el grupo R que en el grupo L, $p < 0{,}0001$. El nivel mediano (rango) alcanzado en el grupo R fue T7 (T5-T10), mientras en el grupo L fue T7 (T4-T10). El tiempo para alcanzar el nivel máximo y para alcanzar un grado 3 en la escala de Bromage fue más breve en el grupo R en comparación con el grupo L, $p < 0{,}0001$. La levobupivacaína produce una duración significativamente más larga (290.50 ± 34.67) del bloqueo motor que la ropivacaína (222.50 ± 23.00). La duración de la analgesia fue significativamente más larga en el grupo L (309.83 ± 36.45) que en el grupo R. No se registraron efectos adversos graves.

Conclusión: La levobupivacaína produce una duración de la analgesia significativamente más larga que la ropivacaína cuando se utiliza en una proporción de 0,6:1. La eficacia, toxicidad y perfil hemodinámico hacen de la ropivacaína un agente adecuado para cirugías con un umbral bajo de hipotensión.

Introduction

Traditionally, bupivacaine has been the drug of choice for the subarachnoid block. However, significantly long duration of action delays recovery of motor function and prolongs post-anaesthesia care unit stay. In addition, several studies have shown that bupivacaine produces higher neurological and cardiac toxicity compared to other local anaesthetics.[1] The problems associated with the toxicity of racemic bupivacaine triggered the development of alternative suitable 'single enantiomeric' local anaesthetic agents with low cardiac and CNS toxicity. Levobupivacaine and Ropivacaine are two relatively new amide local anaesthetic agents that have been produced in order to address the issues of bupivacaine toxicity.

Levobupivacaine is a high potency, long-acting local anaesthetic with a relatively slow onset of action.[2] It has a lower propensity to block inactivated sodium and potassium channels along with faster rate of dissociation compared to its racemic form.[3] The majority of in vitro, in vivo and human pharmacodynamic studies of nerve block indicate that levobupivacaine has similar potency, yet lower risk of cardiovascular and CNS toxicity than bupivacaine.[4] So, having a higher threshold for cardiac and neurotoxicity compared to racemic bupivacaine, anaesthetists feel safer working with levobupivacaine[5] and has the potential to replace bupivacaine

Ropivacaine is the 'S' isomer of the propyl analogue of bupivacaine with longer duration of action, low lipid solubility, low potency and low cardiovascular and CNS toxicity.[7] Ropivacaine blocks nerve fibres involved in pain transmission (Aδ and C fibres) to a greater degree than those controlling motor function (Aβ fibres).[8] Therefore, ropivacaine has been found to induce less intense motor blockade than bupivacaine. Hence, its comparatively shorter duration, faster recovery of motor function and lower toxicity profile have been identified as a potential benefit for surgery of intermediate duration as well as for ambulatory surgery in day care surgical units.

In the present era of evidence-based medicine, each step of our management is thoroughly evaluated by properly controlled, peer-reviewed medical research, and subarachnoid block is not an exception. The concept of a single shot with bupivacaine can do all is now questioned and necessitate the judicious use of safer substitutes. As of Casati et al.[9] theoretical as well as experimental differences do exist in toxicology and clinical profiles due to different anaesthetic potencies of these isomeric forms of bupivacaine, but reflections of these characteristics into clinical practice have not been evident so far. So, we have to explore the typical characteristics and potential uses of these newer drugs. Many studies have been done to compare various forms of bupivacaine, ropivacaine and levobupivacaine. However, most of them have used low doses which may be inadequate for hip surgeries.[10] Fur-

potency ratio between levobupivacaine and ropivacaine was not taken into consideration.[13]

Therefore, this study was conducted to compare the efficacy and characteristics of isobaric forms of intrathecal levobupivacaine 0.5% with ropivacaine 0.75% in equipotent doses for lower limb orthopaedic surgery.

Methodology

Following approval by the Institutional Ethics Committee [(Ref. No. D1303/FM) and Clinical Trial Registry No. (NCT02201784)] and written informed consent, this prospective, randomised, double-blind, controlled, equivalence trial was conducted on sixty ASA grade I/II patients of either sex, aged between 18 and 60 years undergoing spinal anaesthesia for lower limb orthopaedic surgery. Patients with contraindication for spinal anaesthesia, known allergy to local anaesthetic drugs and patients having h/o diabetes, neurological or musculoskeletal diseases that could make our technique difficult were excluded. The patients were randomly divided into two groups of 30 each (group L and group R) by computer-generated randomisation (Fig. 1). Patients in group L received 3 ml levobupivacaine 5 mg/ml (15 mg of LEVO-ANAWIN® 0.5% Neon Laboratories Ltd.) while in group R received 3 ml ropivacaine 7.5 mg/ml (22.5 mg of ROPIN® 0.75% Neon Laboratories Ltd.). All drugs were loaded by an anaesthetist who did not have any involvement in further patient assessment while another anaesthetist administered anaesthesia and assessed all patients. Patients had standard monitoring including electrocardiography, pulse oximetry and non-invasive blood pressure monitoring (NIBP). Baseline heart rate (HR), NIBP and arterial oxygen saturation (SpO_2) were measured. All patients received oxygen via Hudson mask at the rate of 6 l/min until the surgery ends. Intravenous (IV) access was secured, patients were premedicated with i.v. ondansetron 0.1 mg/kg body weight and preloading done with lactated Ringer's (LR) solution 15 ml/kg body weight. Under strict aseptic precautions, skin was infiltrated with lidocaine 2% and lumbar puncture was performed in the sitting position with a 25-G Quincke spinal needle (Becton Dickinson, Madrid, Spain), using a midline approach at the $L_{3–4}$ intervertebral space. Correct needle placement was identified by free flow of CSF and confirmed by aspiration and reinjection of CSF before and after the administration of the study drug solution. The study drug was injected over 20 s. After the injection of the spinal medication, the patients were placed supine immediately, the time of which was recorded as 'zero'. The level of sensory block was assessed every 5 min till the loss of sensation to pinprick, using a 22-guage hypodermic needle with 2 mm protrusion through the guard. Assessments continued at 30 min intervals following the completion of surgery until normal sensation returned. After confirming the loss of sensation at T_{10} dermatome in comparison to $C_{5–6}$ dermatome, patients were given i.v. midazolam 0.03 mg/kg body weight and surgeons were allowed to proceed for the surgery. Inability to achieve T_{10} sensory level within 30 min was considered as 'Failure'. These patients were administered general anaesthesia. They were not included for analysis but only reported as total number of failures according to per protocol analysis. Motor block in the lower limbs was graded according to the modified Bromage scale[14] (Grade 0 = No motor block, Grade 1 = Inability to raise extended leg, able to move knees and feet, Grade 2 = Inability to raise extended leg and move knee, able to move feet, Grade 3 = Complete motor block of the lower limbs). Thereafter, it was performed every 5 min till the attainment of MB grade 3 followed by every 30 min until complete recovery (MB grade 0). HR, NIBP and SpO_2 was

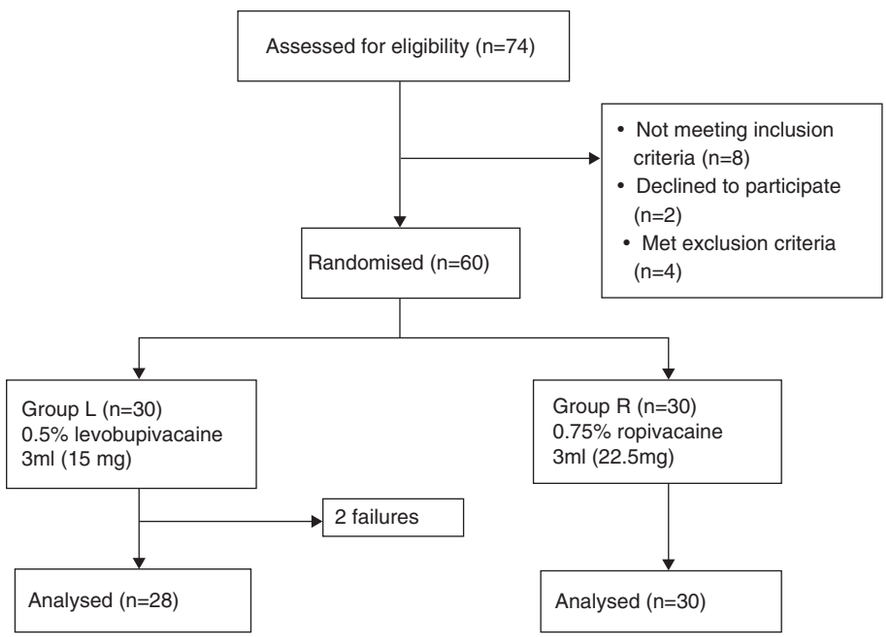

Fig. 1 – CONSORT flow diagram.
***Source*: Authors.**

recorded before induction, every 3 min till 15 min, then, every 15 min until discharge from the recovery room. Hypotension was defined as systolic BP < 90 mmHg and was treated with inj. mephenteramine of 6 mg i.v bolus and fluids. Bradycardia was defined as HR < 50 beats/min and treated with i.v. atropine of 0.5 mg, if symptomatic. For assessment of the onset of anaesthesia, the time for sensory block to develop to T_{10}, maximum block height and time to achieve maximum height were noted. To assess the duration of the sensory block, time for regression to L_1 and duration of analgesia (primary outcome) were compared. Time to achieve maximum motor block, duration of motor block along with any side effects were also noted.

Statistical analysis

Power analysis estimated that a sample size of 30 patients per group would yield 95% power for testing the hypothesis at equivalence margin of 30-min difference in mean time to first analgesic requirement (PS Power and Sample Size Calculator-Version 3.0.43; Dupont WD, Plummer WD). The Type I error probability associated with this test, for the null hypothesis that levobupivacaine and ropivacaine in equipotent doses are similar in terms of duration of analgesia was $\alpha = 0.05$ (Fig. 2). Statistical analysis was performed using Excel 2013 (Microsoft, Redmond, VA), SPSS software (Version 19, SPSS Inc., USA) and Graph Pad Prism 5.00 (Graph Pad Software, San Diego, CA). Data are presented as mean (±SD), median (range), or frequencies (%) as appropriate. Group demographic data and adverse events were compared using unpaired *t*-test or chi-square (χ^2) test, whichever applicable. Comparison of block characteristics, duration of analgesia and haemodynamics were made using unpaired *t*-test. To compare intragroup variations from baseline, one-way ANOVA with Dunnett's multiple comparisons tests was used. A *p*-value of <0.05 was considered statistically significant.

Results

There were no significant differences between the two groups with respect to age, sex, weight, ASA grade or duration of surgery (Table 1). Anaesthesia was successful in all patients except two failures in group L. Onset of anaesthesia to T_{10} was 7.33 ± 2.49 min in group R and 13.50 ± 4.86 min in group L ($p < 0.0001$). The median (range) maximum height achieved in terms of dermatomes in group R was T_7 (T_5–T_{10}) while in group L was T_7 (T_4–T_{10}). The time to reach maximum height was shorter in group R (13.17 ± 3.02 min) as compared to group L (20.33 ± 5.31 min) with a $p < 0.0001$ (Table 2, Fig. 3).

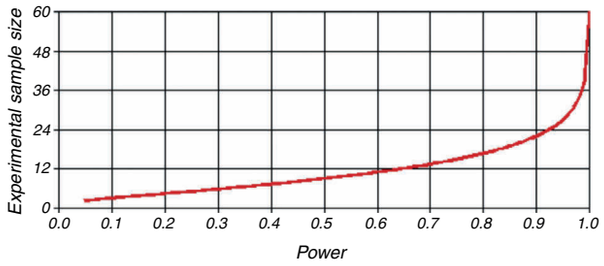

Fig. 2 – Sample size versus power graph for the study.
***Source*: Authors.**

The time to modified Bromage 3 (MB-3) grade was 7.83 ± 2.84 min in group R and 12.17 ± 4.09 min in group L with $p < 0.0001$. Levobupivacaine produced significantly longer duration of motor block (290.50 ± 34.67 min) compared to ropivacaine (222.50 ± 23.00 min), $p < 0.0001$. Time for regression of sensory block to L1 was longer in the group L than group R (251.50 ± 33.12 min versus 191.50 ± 22.86 min; $p < 0.0001$). Duration of analgesia was also significantly longer in group L (309.83 ± 36.45) than group R (249.50 ± 22.83), $p < 0.0001$.

Baseline haemodynamic parameters were comparable in both the groups. The mean MAP decreased significantly in both the groups compared to baseline/preoperative values ($p < 0.05$) but overall incidence of hypotension was not significantly different (Fig. 4a). Furthermore, it was transient (30 min) in ropivacaine group compared to levobupivacaine which was sustained (100 min). There were no significant differences between the two groups with respect to PR and SpO_2 ($p > 0.05$) (Fig. 4b and c).

No incidence of Post Dural Puncture Headache (PDPH) or any other significant adverse effect was observed in either group (Table 3). Hypotension was the most common side effect seen in both the groups, however, total amount of mephentermine used was significantly not different ($p > 0.05$). Bradycardia occurred during intra-op period in 2 patients of each group.

Table 1 – Patient characteristics.

Variable	Group L (*n*)	Group R (*n*)	*p* value
Age (years)	38 ± 17 (30)	35 ± 16 (30)	0.51
Sex (M:F)	24:6 (30)	23:7 (30)	0.99
Weight	53.83 ± 9.44 (30)	57.17 ± 6.65 (30)	0.12
ASA grade I/II	24/6 (30)	24/6 (30)	1.00
Duration of surgery (min)	108 ± 39.47 (28)	93 ± 25.35 (30)	0.09

n, number of patients; M:F, male:female; min, minutes; $p \leq 0.05$ is considered significant.
Source: Authors.

Table 2 – Block characteristics.

Variable	Group L ($n = 28$)	Group R ($n = 30$)	p value
Time to achieve sensory block at T_{10} (min)	13.50 ± 4.94	7.33 ± 2.54	<0.0001
Median maximum level of sensory blockade (range)	T_7 (T_4–T_{10})	T_7 (T_5–T_{10})	–
Time to maximum cephalic spread of sensory block (min)	20.33 ± 5.31	13.17 ± 3.02	<0.0001
Recovery to L_1 (min)	251.50 ± 33.12	191.50 ± 22.86	<0.0001
Duration of analgesia (min)	309.83 ± 36.45	249.50 ± 22.83	<0.0001
Onset of motor block to Bromage 3 (min)	12.17 ± 4.09	7.83 ± 2.84	<0.0001
Duration of motor block (min)	290.50 ± 34.67	222.50 ± 23.00	<0.0001

n, number of patients; "T" is dermatomal level; min, minutes; data are expressed as mean ± SD or median (range); *p*-value <0.05 is considered significant.
Source: Authors.

Discussion

In our study isobaric levobupivacaine showed significantly slower onset of sensory and motor block but with prolonged duration of analgesia compared to ropivacaine.

No significant differences in patient characteristics and baseline haemodynamic parameters were observed between the two groups.

Levobupivacaine and ropivacaine have been produced in order to address the issues of bupivacaine toxicity.[1,15] Several studies have been undertaken in the past to evaluate the clinical efficacy and toxicology of these local anaesthetics in different dosage and baricity. Most of these clinical studies suggested that levobupivacaine was slightly less potent than bupivacaine but more potent than ropivacaine.[16] Higher potency of levobupivacaine than ropivacaine could partly be explained by its greater lipid solubility and formulation[17] which underestimates the active molecules by 12.6% than its racemate.[18] However, many recent studies[19,20] have found greater than 30% difference in potency which implies that levobupivacaine is actually more potent than ropivacaine. Its potency compared to ropivacaine remained inconsistent and varied from 1 to 1.67.[17] So, based on the above facts and various previous studies,[7,19,21,22] we assumed levobupivacaine to be 1.5 times more potent than ropivacaine.

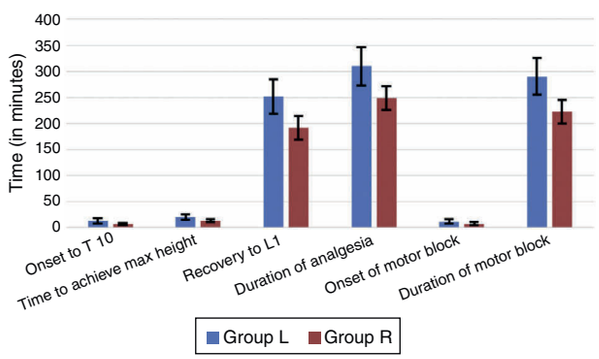

Fig. 3 – Block characteristics.
***Source*: Authors.**

Previous authors have used different doses (5–17.5 mg) of levobupivacaine.[11,12,23,24] Taking into consideration the previous studies,[11–13] MLAC and potency ratio we have used levobupivacaine 15 mg (5 mg ml^{-1}) to compare ropivacaine 22.5 mg (7.5 mg ml^{-1}), so as to achieve adequate sensory and motor block for most of the orthopaedic procedures.

There is gross variation in the findings of various authors regarding sensory block onset time. According to some authors, there is no significant difference in onset time.[11–13,24] Contrary to this, some are of the opinion that there is significant difference in the onset time of two drugs.[23,25,26] However, in the present study, ropivacaine achieved sensory level of T_{10} significantly faster than levobupivacaine consistent with the past researches.[23,25,26] The variations in the finding of these studies could be due to sample size, demographic profile, methodology, drug dose and baricity. Cuvas et al.[27] has only taken elderly (>60 yrs) males while Sananslip et al.[28] recruited females posted for gynaecological surgery.

In the present study, both groups achieved the median dermatomal height of T_7 but levobupivacaine took longer time to achieve maximum block level than ropivacaine. Furthermore, levobupivacaine (T_4–T_{10}) showed slightly greater variability compared to ropivacaine (T_5–T_{10}). According to most of the authors,[12,21,23,26–29] median height attained was in the range of T_8–T_9 with similar dosing and technique. Nevertheless, few authors[11,12] obtained varied results which may be attributed

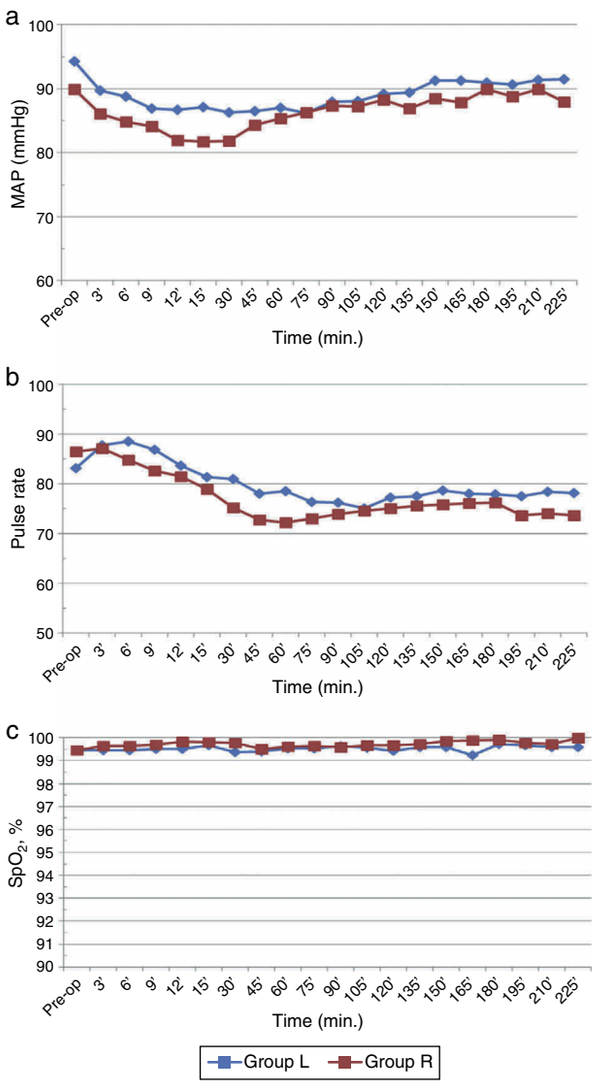

Fig. 4 – (a) Mean arterial pressure variation with time. (b) Pulse rate variation with time. (c) SpO_2 variation with time. *Source*: Authors.

to different doses and baricity of the ropivacaine used in their study.

Similar to the sensory blockade, ropivacaine also showed faster onset of motor blockade compared to levobupivacaine. However, Khaw et al.[30] used a measured isobaric preparation of ropivacaine for spinal anaesthesia in right lateral position administered over 60 s did not find any significant difference. As we have not measured the specific gravity of the drug in our study, taking into consideration the fact that bupivacaine and ropivacaine are hypobaric at 37 °C,[31] it can be assumed that the hypobaric nature of our drug, sitting position[32,33] and comparatively faster rate of injection[29] has resulted in quicker onset of motor blockade.

In our study, sensory (L_1) and motor regression of ropivacaine was comparatively faster than levobupivacaine. Various authors in the past obtained similar results with ropivacaine showing faster sensory[11,24,25] and motor recovery.[13,23,27]

Ropivacaine and levobupivacaine, apart from being slightly different in potencies, are assumed to be almost similar in clinical hands.[9] But the present study showed that even at equipotent doses of 1.5:1 (Ropi:Levo), ropivacaine offer significantly shorter duration of analgesia compared to levobupivacaine. This was similar to the findings of previous authors who showed early regression of ropivacaine as compared to levobupivacaine.[12,23,34] However, Gautier et al.[35] documented no difference while comparing 12 mg ropivacaine with 8 mg levobupivacaine in Caesarean section. Different pharmacodynamic response due to lower dose and different study population seems to be the most reasonable explanation for this discrepancy.

Decrease in MAP and PR are two most frequently encountered complications of neuraxial blocks. In our study, it was observed that fall in BP was transient in ropivacaine group but sustained in levobupivacaine group. In spite of this, there was no significant difference in the overall incidence of hypotension and these were promptly treated without any serious consequences. Further, the total mephentermine dose required in both the groups were comparable ($p > 0.05$). However, the higher incidence of transient hypotension seen with ropivacaine could arise due to quicker attainment of maximum height of block in comparison to levobupivacaine resulting in fall blood pressure. This was in accordance with the opinion of Carpenter et al.[36]

Extreme care and vigilance were taken to avoid biases by making the study randomised and double blind. However, biases and limitations often creep during research and this study is not an exception. Study design might have led certain degree of biases to sneak in as we used per protocol analysis. An important limitation of our study was that we did not measure the specific gravity of either of the drug. Maintenance of temperature could be a problem in tropical countries which could have influenced the overall results.[30] Besides, higher sodium concentration and osmolality of levobupivacaine further increases its density. The quality of anaesthesia was also not measured in the study.

Table 3 – Adverse effects.

Variable	Group L ($n = 28$)	Group R ($n = 30$)	p value
Nausea/vomiting	4/0 (14/%)	2/0 (7%)	0.42
Hypotension	7 (25%)	10 (33%)	0.57
Bradycardia	2 (7%)	2 (7%)	0.99
Shivering	3 (11%)	5 (17%)	0.71

n, number of patients; $p \leq 0.05$ is considered significant.
Source: Authors.

Conclusion

We, therefore, conclude that isobaric levobupivacaine and ropivacaine doses used in the study produce adequate anaesthesia and analgesia for lower limb orthopaedic surgery without any serious side effects. Levobupivacaine produces significantly longer duration of analgesia than ropivacaine when used in a ratio of 0.6:1. Hence, drugs should be used taking into consideration the condition of patient, nature and

duration of surgery. Efficacy, toxicity and haemodynamic profile make ropivacaine suitable agent for day care and other surgeries with low threshold for hypotension, while levobupivacaine can be a suitable agent for prolonged surgeries.

Funding

None.

Conflicts of interest

None declared.

REFERENCES

1. Dony P, Dewinde V, Vanderick B, Cuignet O, Gautier P, Legrand E, et al. The comparative toxicity of ropivacaine and bupivacaine at equipotent doses in rats. Anesth Analg. 2000;91:1489–92.
2. Buckenmaier CC 3rd, Bleckner LL. Anaesthetic agents for advanced regional anaesthesia: a North American perspective. Drugs. 2005;65:745–59.
3. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology. 1985;62:396–405.
4. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs. 2000;59:551–79.
5. Arias MG. Levobupivacaine: a long acting local anaesthetic, with less cardiac and neurotoxicity. Update Anaesth. 2002:14.
6. Whiteside JB, Wildsmith JAW. Spinal anaesthesia with ropivacaine 5 mg/ml in glucose 10 mg/ml or 50 mg/ml. Br J Anaesth. 2001;86:241–4.
7. Malinovsky JM, Charles F, Kick O, Lepage JY, Malinge M, Cozian A, et al. Intrathecal anesthesia: ropivacaine versus bupivacaine. Anesth Analg. 2000;91:1457–60.
8. Wille M. Intrathecal use of ropivacaine: a review. Acta Anaesthesiol Belg. 2004;55:251–9.
9. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different. Best Pract Res Clin Anaesthesiol. 2005;19:247–68.
10. Sell A, Olkkola KT, Jalonen J, Aantaa R. Minimum effective local anaesthetic dose of isobaric levobupivacaine and ropivacaine administered via a spinal catheter for hip replacement surgery. Br J Anaesth. 2005;94:239–42.
11. Casati A, Moizo E, Marchetti C, Vinciguerra F. A prospective, randomized, double-blind comparison of unilateral spinal anesthesia with hyperbaric bupivacaine, ropivacaine, or levobupivacaine for inguinal herniorrhaphy. Anesth Analg. 2004;99:1387–92.
12. Cappelleri G, Aldegheri G, Danelli G, Marchetti C, Nuzzi M, Iannandrea G, et al. Spinal anesthesia with hyperbaric levobupivacaine and ropivacaine for outpatient knee arthroscopy: a prospective, randomized, double-blind study. Anesth Analg. 2005;101:77–82.
13. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anesthesia: comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. Acta Anaesthesiol Belg. 2008;59:65–71.
14. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders; 1978. p. 144.
15. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. Acta Pharmacol Toxicol. 1972;31:444–50.
16. Sanford M, Keating GM. Levobupivacaine: a review of its use in regional anaesthesia and pain management. Drugs. 2010;70:761–91.
17. Frawley G, Smith KR, Ingelmo P. Relative potencies of bupivacaine, levobupivacaine, and ropivacaine for neonatal spinal anaesthesia. Br J Anaesth. 2009;103:731–8.
18. Rosenberg PH, Schug SA. Levobupivacaine base and levobupivacaine hydrochloride. Br J Anaesth. 2005;94:544.
19. Lee YY, Ngan Kee WD, Fong SY, Liu JTC, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. Anesth Analg. 2009;109:1331–4.
20. Parpaglioni R, Frigo MG, Lemma A, Sebastiani M, Barbati G, Celleno D. Minimum local anaesthetic dose (MLAD) of intrathecal levobupivacaine and ropivacaine for Caesarean section. Anaesthesia. 2006;61:110–5.
21. Gautier PE, De Kock M, Steenberge AV, Poth N, Lahaye-Goffart B, Fanard L, et al. Intrathecal ropivacaine for ambulatory surgery: a comparison between intrathecal bupivacaine and intrathecal ropivacaine for knee arthroscopy. Anesthesiology. 1999;91:1239–45.
22. Leone S, Cianni SD, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anesthetics, ropivacaine and levobupivacaine. Acta Biomed. 2008;79:92–105.
23. Glaser C, Marhofer P, Zimpfer G, Heinz MT, Sitzwohl C, Kapral S, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg. 2002;94:194–8.
24. Breebaart MB, Vercauteren MP, Hoffmann VL, Adriaensen HA. Urinary bladder scanning after day-case arthroscopy under spinal anaesthesia: comparison between lidocaine, ropivacaine, and levobupivacaine. Br J Anaesth. 2003;90:309–13.
25. McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson KRU. Spinal anaesthesia: comparison of plain ropivacaine 5 mg/ml with bupivacaine 5 mg/ml for major orthopaedic surgery. Br J Anaesth. 2002;89:702–6.
26. Vanna O, Chumsang L, Thongmee S. Levobupivacaine and bupivacaine in spinal anesthesia for transurethral endoscopic surgery. J Med Assoc Thail. 2006;89:1133–9.
27. Cuvas O, Basar H, Yeygel A, Turkyýlmaz E, Sunay MM. Spinal anesthesia for transurethral resection operations: levobupivacaine with or without fentanyl. Middle East J Anaesthesiol. 2010;20:547–52.
28. Sanansilp V, Trivate T, Chompubai P, Visalyaputra S, Suksopee P, Permpolprasert L, et al. Clinical characteristics of spinal levobupivacaine: hyperbaric compared with isobaric solution. Sci World J. 2012:1–7.
29. McClure JH, Brown DT, Wildsmith JAW. Effect of injected volume and speed of injection on the spread of spinal anesthesia with isobaric amethocaine. Br J Anaesth. 1982;54:917.
30. Khaw KS, Ngan Kee WD, Wong M, Floria Ng, Lee A. Spinal ropivacaine for cesarean delivery: a comparison of hyperbaric and plain solutions. Anesth Analg. 2002;94:680–5.
31. McLeod GA. Density of spinal anaesthetic solutions of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose. Br J Anaesth. 2004;92:547–51.
32. Tsai T, Greengrass R. Spinal anesthesia. In: Hadzic A, editor. Textbook of regional anesthesia and acute pain management. 1st ed. McGraw-Hill; 2007. p. 194–221.
33. Brown DL. Spinal, epidural, and caudal anesthesia. In: Miller RD, editor. Miller's anesthesia. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2009. p. 1611–38.

34. Delfino J, Pontes S, Gondim D, Vale NB. Isobaric 0.5% bupivacaine and 0.5% ropivacaine in spinal anesthesia for orthopedic surgery – a comparative study. Rev Bras Anestesiol. 1999;49:160–4.
35. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. Br J Anaesth. 2003;91:684–9.
36. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992;76:906–16.