A COMPARATIVE STUDY OF LEVOBUPIVACAINE 0.5% AND BUPIVACAINE 0.5% IN EPIDURAL ANAESTHESIA IN ELECTIVE LOWER LIMB SURGERIES IN ADULTS

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ABSTRACT

BACKGROUND

Bupivacaine produces fatal cardiotoxic and neurotoxic effects following accidental intravascular injection due to its R (+) enantiomer. Levobupivacaine, the pure S (-) enantiomer of bupivacaine, is found to be less toxic than its racemic parent and might be a safer alternative.

The aim of this study was to compare the efficacy of Levobupivacaine 0.5% and Bupivacaine 0.5% in epidural anaesthesia in elective lower limb surgeries in adults with respect to onset and maximum dermatomal level of sensory blockade, duration of analgesia, onset, intensity and duration of motor blockade, haemodynamic parameters and perioperative complications.

Settings and Design- A prospective, randomised, comparative study.

MATERIALS AND METHODS

A study was conducted on 60 ASA I-II patients, aged 18 - 60 years of either sex posted for elective lower limb surgeries after ethical clearance and patient's written informed consent. The patients were assigned randomly (using computer generated randomisation) to receive epidurally either 12 mL of bupivacaine 0.5% as Group B (n= 30) or to receive 12 mL of levobupivacaine 0.5% as Group L (n= 30). Onset and maximum dermatomal level of sensory blockade, duration of analgesia, onset, intensity and duration of motor blockade and haemodynamic parameters were assessed. Perioperative complications were identified and treated accordingly. Study concluded when the patient first complained of pain.

Statistical Analysis- The study was analysed by Chi-square and student's 't' tests ($p < 0.05$: statistically significant) and by using SPSS (Ver. 10.0.5) package.

RESULTS

The time of onset of motor blockade was prolonged in Group L when compared to Group B (B- 16.50 ± 2.921 min and L- 19.60 ± 4.889 min; $p = 0.004$). The intensity of motor blockade was greater in Group B when compared to Group L (B- 2.17 ± 0.379 and L- 1.93 ± 0.450 ; $p = 0.034$). No statistically significant difference was noted in terms of onset and maximum dermatomal level of sensory blockade, duration of analgesia, duration of motor blockade, haemodynamic parameters and perioperative complications between both the groups.

CONCLUSION

Levobupivacaine 0.5% could prove to be a good alternative, as it produces a sensory blockade, haemodynamic and side effect profile equivalent to Bupivacaine 0.5% in lower limb surgeries. In terms of motor blockade, the onset is delayed and is less dense with levobupivacaine as compared to bupivacaine but with a similar duration.

KEYWORDS

Epidural Anaesthesia; Bupivacaine; Levobupivacaine; Lower Limb Surgeries; Clinical Efficacy.

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BACKGROUND

Epidural anaesthesia is a versatile regional anaesthetic technique widely used in practice, which over spinal anaesthesia has the advantages such as it provides effective surgical anaesthesia which can be prolonged with postoperative

analgesia, segmental blockade and better haemodynamic stability.^{1,2} Different local anaesthetics are used for epidural anaesthesia namely lignocaine, bupivacaine, ropivacaine and now levobupivacaine.

Bupivacaine is a long-acting local anaesthetic, which shows good motor/sensory separation.³ It has a chiral centre in its structure and hence exhibits stereoisomerism. It is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, levobupivacaine S (-) isomer and dextrobupivacaine R (+) isomer. While these two molecules have identical physicochemical properties, they have distinct pharmacological and toxicological effects.⁴ Although, bupivacaine has been safely used in regional anaesthesia for many years, fatal cardiotoxic and neurotoxic effects which have been linked to its R (+) isomer may be seen following its accidental intravascular injection. Therefore, pure S (-) enantiomers of bupivacaine, i.e. ropivacaine and levobupivacaine with fewer toxic effects

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were thus introduced into clinical anaesthesia practice.⁵⁻⁷

Levobupivacaine has emerged in recent years as a safer alternative for regional anaesthesia than its racemic parent. The affinity of the S (-) isomer to the cardiac sodium channel in the inactive state is lower than that of the R (+) isomer of bupivacaine. Reports of its cardiotoxicity and neurotoxicity are scarce. The occasional toxic symptoms with its use are usually reversible with minimal treatment with no fatal outcome. Hence, levobupivacaine has a potentially greater margin of safety than racemic bupivacaine and can prove to be a better alternative to bupivacaine.⁸⁻¹³

Hence, this study is undertaken to compare the effectiveness of Levobupivacaine 0.5% with Bupivacaine 0.5% for epidural anaesthesia in elective lower limb surgeries.

MATERIALS AND METHODS

Source of Data

The present study titled "A comparative study of levobupivacaine 0.5% and bupivacaine 0.5% in epidural anaesthesia in elective lower limb surgeries in adults" was conducted in the Department of Anaesthesiology and Critical Care, Kempegowda Institute of Medical Sciences and Research Centre, Bengaluru from December 2013 to July 2015.

Type of Study

A prospective, randomised, comparative study.

Power Analysis

A post-hoc power analysis was carried out using PASS-11 Software.¹⁴ The mean time of onset of motor blockade in Group B was 16.50 ± 2.921 min and that in Group L was 19.60 ± 4.889 min. The Group sample sizes of 30 and 30 achieve 85% power to detect a difference of -3.10 between the groups with a significance level (alpha) of 0.05 using a two-sided two-sample t-test.

Sampling Method

Patients were randomised to treatment group using computer generated randomisation.

Statistical Analysis

The study was analysed by Chi-square and student's 't' tests ($p < 0.05$: statistically significant). Data was entered in Microsoft Excel and analysed using SPSS (Statistical Package for Social Science, Ver. 10.0.5) package.

Method of Collection of Data

After ethical clearance and written informed consent from the patients a prospective, randomised, comparative study was conducted in 60 patients of ASA Grade 1 and 2 aged between 18 to 60 years of either sex posted for elective lower limb surgeries.

Inclusion Criteria

Patients with an age group of 18 to 60 years of either sex, ASA Grades 1 and 2, patients posted for elective lower limb surgeries, patients with height between 150 – 180 cm and weight between 50 – 80 kg.

Exclusion Criteria

Patient's refusal for regional anaesthesia, known allergy to local anaesthetics, pregnant and lactating women, morbidly obese patients and patients having the following: Local infection, severe hypovolaemia, bleeding diathesis and coagulopathy, uncontrolled hypertension and diabetes mellitus, neurological disorders, raised intracranial tension, deformities of spine and hepatic diseases.

The study population was thus selected based on the above criteria and then randomly divided into two groups of 30 patients in each group based on the study drug given as follows-

1. Group L (n= 30) – 12 mL of levobupivacaine 0.5% epidurally.
2. Group B (n= 30) – 12 mL of bupivacaine 0.5% epidurally.

Procedure

Preoperative assessment was done for each patient and written informed consent was taken. Patients were fasted for at least 8 hours before the procedure. On the day of surgery, intravenous line was secured with 18-G cannula in upper limb. Patients were monitored using automated multiparameter monitor. Basal vital parameters like heart rate, blood pressure, respiratory rate and SPO2 were noted.

Patients were placed in a lateral position. Under strict asepsis, the skin at the L2-L3/L3-L4 level was infiltrated with 2 mL of Inj. Lignocaine 2%. Epidural space was identified with loss of resistance to air technique at the desired level using 18-G Tuohy's needle. An epidural catheter was advanced in cephalad direction into epidural space for 3 cm and fixed. Test dose of 3 mL of Inj. Lignocaine 2% with Adrenaline 1:200000 was given after negative aspiration for CSF and blood. This was to exclude the presence of needle in the subarachnoid space and epidural vessels. After confirming the correct position of the catheter, patient was turned to supine position. Five minutes after the test dose when there was no evidence of subarachnoid or intravascular injection, 12 mL of study drug was given at a rate of 1 mL/3 secs through the catheter.

Intraoperatively, the following Parameters were Monitored

- Onset of sensory blockade.
- Maximum dermatomal level of sensory blockade.
- Duration of analgesia.
- Onset of motor blockade.
- Maximum intensity of motor blockade (using Modified Bromage scale).
- Duration of motor blockade.
- Haemodynamic changes- SpO2, heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure. All the parameters were recorded every minute for the first 5 minutes, every 5 minutes till the end of 1 hour and then every 15 minutes till the end of surgery.
- Intraoperative and postoperative complications if any- such as nausea, vomiting, hypotension, bradycardia and respiratory depression was looked for, recorded and treated accordingly.

After the surgery, patients were referred to the post anaesthesia care unit where they stayed until there was

complete recovery of sensory and motor blockade. Postoperatively, vital parameters were recorded every 15 minutes. Duration of analgesia, duration of motor blockade and any adverse events were noted. Study concluded when the patient first complained of pain after the administration of the drug under study epidurally. Continuous epidural infusion was given as Inj. Bupivacaine 0.125% with 1 µg of Inj. Fentanyl in each mL of local anaesthetic for the next 72 hours postoperatively.

Definitions

Onset of Sensory Blockade

It is the time taken from the completion of the injection of study drug till the patient does not feel the pinprick at L1 level.

Maximum Dermatomal Level of Sensory Blockade

It is defined as the highest dermatomal level, at which the patient does not feel the pinprick after completion of the injection of the study drug.

Duration of Analgesia

It is taken from the time of injection of the study drug till the patient complains of pain at the site of surgery.

Onset of Motor Blockade

It is taken from the completion of the injection of study drug till the patient develops Modified Bromage Scale Grade 1.

Maximum Intensity of Motor Blockade

It is defined as the maximum intensity of motor blockade attained after completion of the injection of the study drug.

Duration of Motor Blockade

It is taken from the time of injection of the study drug till the patient develops Modified Bromage Scale Grade 0.

Hypotension

It was defined as reduction of systolic blood pressure more than 30% below baseline value or mean blood pressure less than 90 mmHg. Hypotension was treated with Inj. Ephedrine 6 mg IV in bolus doses and increased administration of intravenous fluids.

Bradycardia

It was defined as heart rate less than 50/minute and was treated with Inj. Atropine 0.6 mg IV.

Modified Bromage Scale:¹⁵

- 0: No motor block.
- 1: Inability to raise extended leg; able to move knees and feet.
- 2: Inability to raise extended leg and move knee; able to move feet.
- 3: Complete block of motor limb.

RESULTS

In the present study, we found that both the study groups were comparable with respect to age, height, weight (Table 1), gender, ASA grade (Table 2) and duration of surgery (Table 3).

The mean time of onset of sensory blockade in Group B was 11.43 ± 2.431 min and that in Group L was 12.37 ± 2.157 min. Hence, with a 'p' value of 0.121 there was no statistically significant difference between both the groups in this regard (Table 4).

The mean time of onset of motor blockade in Group B was 16.50 ± 2.921 min and that in Group L was 19.60 ± 4.889 min. Hence, with a 'p' value of 0.004 ($p < 0.05$ is significant), there was a statistically significant difference between both the groups in this regard. That is the onset of motor blockade was faster with bupivacaine when compared to levobupivacaine (Table 4).

Among patients in Group B 13.3% attained a level of T8, T9 and T12 each, 36.7% attained a level of T10 and 23.3% attained a level of T11. Among patients in Group L 20% attained a level of T8, 6.7% a level of T9, 33.3% a level of T10, 13.3% a level of T11 and 26.7% a level of T12. There was no significant difference in the maximum dermatomal level of sensory blockade achieved in both the groups, as indicated by 'p' value of 0.514 (Table 4).

In Group B there were 25 patients (83.3%) with Grade 2 motor block and 5 patients (16.7%) with Grade 3 and none with Grades 0 and 1. In Group L 4 patients (13.3%) had Grade 1 block, 24 patients (80%) had Grade 2 block, 2 patients (0.07%) had Grade 3 and none had Grade 0. The mean maximum intensity of motor blockade in Group B was 2.17 ± 0.379 and that in Group L was 1.93 ± 0.450 . Hence, with a 'p' value of 0.034 ($p < 0.05$ is significant), there was a statistically significant difference between both the groups in this regard. That is bupivacaine group achieved a greater intensity of motor blockade when compared to the levobupivacaine group (Table 4).

The mean duration of analgesia in Group B was 195.17 ± 22.685 min and that in Group L was 194.50 ± 21.907 min. Hence, there is no significant difference between both the groups in this regard as indicated by a 'p' value of 0.908 (Table 4).

The mean duration of motor blockade in Group B was 174.83 ± 22.302 min and that in Group L was 174.00 ± 20.146 min. Hence, there is no significant difference between both the groups with respect to the duration of motor blockade as indicated by a 'p' value of 0.880 (Table 4).

There was no significant difference between bupivacaine and levobupivacaine groups with respect to SpO₂, HR, SBP, DBP and MBP recorded at timed intervals and with respect to perioperative complications (Table 5).

Variables		Group B	Group L	P value
Age (in years)	Mean ± SD	38.3±13.370	38.3±13.603	1.000
Height (in cm)	Mean ± SD	167.2 ± 6.420	166.9 ± 5.996	0.836
Weight (in kg)	Mean ± SD	67.3±5.388	66.5± 5.463	0.586

Table 1. Comparison of Demographic Data between the Study Groups

Variables		Group B		Group L		X ²	P value
		No	%	No	%		
Gender	Male	21	70.0	23	76.7	0.341	0.559
	Female	9	30.0	7	23.3		
	Total	30	100	30	100		
ASA Grade	Grade 1	22	73.3	19	63.3	0.693	0.405
	Grade 2	8	26.7	11	36.7		
	Total	30	100	30	100		

Table 2. Distribution of Gender and ASA Grade in the Study Groups

	Group B Mean ± SD	Group L Mean ± SD
Duration of Surgery (min)	178.67 ± 33.834	174.83 ± 38.807
't' value	0.166	
'p' value	0.685	

Table 3. Mean Values of Duration of Surgery in the Study Groups

Study Variables	Group B (Mean ± SD)	Group L (Mean ± SD)	P value
Onset of Sensory Blockade (min)	11.43±2.431	12.37 ± 2.157	0.121
Onset of Motor Blockade (min)	16.50±2.921	19.60 ± 4.889	0.004
Maximum Dermatome Level of Sensory Blockade	T ₈ -T ₁₂	T ₈ -T ₁₂	0.514
Maximum Intensity of Motor Blockade (using Modified Bromage Scale)	2.17±0.379	1.93 ± 0.450	0.034
Duration of Sensory Blockade (min)	195.17 ± 22.685	194.50 ± 21.907	0.908
Duration of Motor Blockade (min)	174.83 ± 22.302	174.00 ± 20.146	0.880

Table 4. Comparison of Characteristics of Block between the Study Groups

Perioperative Complication	Group B		Group L	
	No.	%	No.	%
Nausea/Vomiting	4	13.3	2	6.7
Hypotension	0	0	0	0
No Complication	26	86.7	28	93.3
Total	30	100	30	100
X ²	0.741			
'p' value	0.389			

Table 5. Comparison of Perioperative Complications in the Study Groups

Graph 1. Comparison of Mean Values of Time of Onset of Sensory Blockade

Graph 2. Comparison of Mean Values of Time of Onset of Motor Blockade

Graph 3. Comparison of Mean Values of Maximum Dermatome Level of Sensory Blockade

Graph 4. Comparison of Mean Values of Maximum Intensity of Motor Blockade

Graph 5. Comparison of Mean Values of Duration of Analgesia

Graph 6. Comparison of Mean Values of Duration of Motor Blockade

Graph 7. Comparison of Mean Values of Perioperative Complications

DISCUSSION

Bupivacaine produces fatal cardiotoxic and neurotoxic effects following accidental intravascular injection, which is attributed to its R (+) isomer, thus showing enantioselectivity in producing toxicity. Levobupivacaine a pure S (-) enantiomer of bupivacaine has been found to be less cardiotoxic and less neurotoxic in various preclinical studies when compared to bupivacaine. Hence, levobupivacaine has a safer pharmacological profile and has emerged as a safer alternative for regional anaesthesia than its racemic parent.³⁻⁹

The aim of this study was to compare the efficacy of levobupivacaine 0.5% and bupivacaine 0.5% in epidural anaesthesia in elective lower limb surgeries in adults with

respect to onset and maximum dermatomal level of sensory blockade, duration of analgesia, onset, intensity and duration of motor blockade, haemodynamic parameters and perioperative complications.

The present study consisted of 60 patients aged between 18 - 60 years of either sex, ASA Grade 1 - 2 undergoing epidural anaesthesia for elective lower limb surgeries. The study population was divided into two groups of 30 each based on the study drug used in each group as:

- Group L (n= 30)- 12 mL of isobaric levobupivacaine 0.5% epidurally.
- Group B (n= 30)- 12 mL of isobaric bupivacaine 0.5% epidurally.

In the present study, both the groups were comparable with respect to age, height, weight, gender, ASA grade and duration of surgery.

Surav DB et al¹⁶ found that 10 mL of 0.5% levobupivacaine plus 5 mL of 0.9% saline produces a block clinically comparable to that of 10 mL of 0.75% levobupivacaine plus 5 mL of 0.9% saline for transurethral resection of prostate surgery. Hence, we have used 0.5% levobupivacaine in our study.

The study drug volume of 12 mL was calculated based on the amount of drug required per segment in the lumbar region.¹⁷

Fesih Kara et al,⁵ Kopacz et al,¹⁸ Cox CR et al¹⁹ and Casati A et al²⁰ in their respective studies found that there was no significant difference between the bupivacaine and levobupivacaine groups with respect to time of onset of sensory blockade, which is similar to our study.

Kopacz et al¹⁸ found that the levobupivacaine group showed a significantly slower onset of motor blockade with only 4 out of 28 patients (14%) having detectable blockade after 30 mins compared with 20 out of 28 patients (71%) in the bupivacaine group. Hence, with a $p < 0.001$ there was significant difference between both the groups in this regard, which is similar to our study.

Cox CR et al¹⁹ in 1998 in their study titled 'Extradural S (-)-bupivacaine: comparison with racemic RS-bupivacaine' found that the time of onset of motor blockade in bupivacaine (racemic RS-bupivacaine 0.5%) group was 17.0 ± 7.0 min and that in levobupivacaine (S (-)-bupivacaine 0.5%) group was 25.0 ± 23.0 min. Hence, there was a significant difference between both the groups in this regard with bupivacaine producing a faster onset of motor blockade than levobupivacaine, which is similar to our study.

Kopacz et al,¹⁸ Cox CR et al,¹⁹ Casati A et al²⁰ and Pedro Paulo Tanaka TSA et al²¹ in their respective studies found that there was no significant difference between bupivacaine and levobupivacaine with respect to the maximum dermatomal level of sensory blockade achieved, which is similar to our study. The peak block height was between T5 and T6 in both treatment groups.

Cox CR et al¹⁹ found that in the S (-) bupivacaine 0.5% (levobupivacaine) group, 14 out of 29 patients did not develop motor blockade. This is in accordance with our study where levobupivacaine group achieved a lesser intensity of motor blockade when compared to bupivacaine group.

Kopacz et al¹⁸ found that in levobupivacaine group, only 4 out of 28 patients (14%) had detectable blockade after 30 mins compared with 20 out of 28 patients (71%) in the bupivacaine group ($p < 0.001$). This is in accordance with our

study, where levobupivacaine group attained a lesser intensity of motor blockade when compared to bupivacaine group.

Casati A et al²⁰ found that complete motor block (modified Bromage score ≥ 2) was observed in all patients of bupivacaine group (100%) and 12 patients of Levobupivacaine group (80%), which is in accordance with our study where levobupivacaine group attained a lesser intensity of motor blockade when compared to bupivacaine group.

Pedro Paulo Tanaka TSA et al²¹ found that there was statistically significant difference in Modified Bromage level 2 blockade in racemic bupivacaine group as compared to the levobupivacaine group, which is similar to our study.

Fesih Kara et al,⁵ Kopacz et al,¹⁸ Cox CR et al¹⁹ and Casati A et al²⁰ in their respective studies found that there was no significant difference between the bupivacaine and levobupivacaine groups with respect to duration of analgesia and duration of motor blockade, which is similar to our study.

In the present study, we found that there was no significant difference between both the groups with respect to SpO₂, HR, SBP, DBP, MBP and perioperative complications which is in accordance with studies done by Fesih Kara et al,⁵ Kopacz et al,¹⁸ Cox CR et al¹⁹ and Casati A et al.²⁰

CONCLUSION

Based on the present clinical comparative study, we conclude that Levobupivacaine 0.5%, when administered through epidural route provides adequate anaesthesia for elective lower limb surgeries comparable to Bupivacaine 0.5% at equal doses. Levobupivacaine achieves a sensory blockade-onset, maximum dermatomal level attained and duration of analgesia comparable to bupivacaine. The duration of motor blockade, haemodynamic parameters and perioperative complications were similar between the two drugs. However, slower onset and lesser intensity of motor blockade were observed with levobupivacaine when compared to bupivacaine.

Hence, we conclude that Levobupivacaine 0.5% can be used as a safer alternative to Bupivacaine 0.5% for epidural anaesthesia in lower limb surgeries.

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