A COMPARATIVE STUDY OF INTRATHECAL HYPERBARIC 0.5% BUPIVACAINE VERSUS INTRATHECAL 0.5% ISOBARIC LEVOBUPIVACAINE

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ABSTRACT

BACKGROUND

Bupivacaine is a long-acting agent capable of producing prolonged anaesthesia and analgesia that can be prolonged even further by the addition of epinephrine. It is substantially more cardiotoxic than lidocaine. The cardiotoxicity of bupivacaine is cumulative and substantially greater than would be predicted by its LA potency. At least part of the cardiotoxicity of bupivacaine maybe mediated centrally because direct injection of small quantities of bupivacaine into the medulla can produce malignant ventricular arrhythmias. Bupivacaine-induced cardiotoxicity can be difficult to treat.[1] Levobupivacaine contains a single enantiomer of bupivacaine hydrochloride and is less cardiotoxic than bupivacaine. It is extensively metabolised with no unchanged drug detected in urine or faeces. Research results suggest that levobupivacaine is a suitable less toxic alternative to bupivacaine.[2]

METHODS

The study entitled "A Randomised Controlled Double-Blind Comparative Study of 0.5% Levobupivacaine vs. 0.5% Heavy Bupivacaine For Surgeries Below Umbilicus During Spinal Anaesthesia" for various procedures done in the Department of Anaesthesiology at Andhra Medical College at King George Hospital, Visakhapatnam, from November 2011 to October 2012. The study was undertaken after obtaining Hospital Ethics Committee clearance as well as written informed consent from all patients after explaining and reassuring about the spinal procedure. A total of 100 patients of both sexes scheduled for elective lower abdominal surgeries under spinal anaesthesia in the age group of 18 to 55 years and belonging to American Society of Anaesthesiologists (ASA) Physical Status I and II were enrolled for the study. The enrolled patients were randomised to one of the two groups of equal-sized prospective, comparative study group using a double-blind protocol design Group B (n=50) received 3.0 mL volume of 0.5% hyperbaric bupivacaine intrathecally and Group L (n=50) received 3.0 mL volume of 0.5% isobaric levobupivacaine intrathecally. Routine preanaesthetic checkup of all the patients was done to exclude coexisting medical conditions and to assess airway and spine. Routine investigations like haemoglobin%, blood group and typing, urine examination, etc. were done.

RESULTS

The mean time of onset of sensory blockade in group B is 1.78±0.708 mins. and in group L is 2.5±0.863 mins. There is no clinical significance between group B and L regarding mean time for onset of sensory blockade. Five out of 50 in group B, twelve out of 50 in group L attained level T_4 of sensory blockade. Nineteen out of 50 in group B and fourteen out of 50 in group L attained T_6, nineteen out of 50 and seventeen out of 50 attained level T_8. Five out of 50 and seven out of 50 attained T_9 level of sensory blockade. Two out of 50 in group B and none from group L attained T_{10} level of sensory blockade. The mean time taken for attaining maximum sensory blockade is 8.98±1.477 mins. in Group B and 8.08±1.70 mins. in group L. There is no clinical significant difference between group B and L regarding the mean time for attaining maximum sensory blockade. The mean time taken for regression of sensory blockade by two segments is 86.3±6.22 mins. in group B and 86.0±6.08 mins. in group L. The mean duration of analgesia for group B is 161.0±12.66 mins. and group L is 164.20±9.55 mins. The mean duration of sensory regression to S_1 in group B is 201.2±12.59 mins. and in group L is 200.7±12.25 mins. The mean time taken for the onset of motor blockade is 1.98±0.55 mins. in group B and in group L is 2.08±0.70 mins. The mean time taken for attaining maximum motor blockade in group B is 6.56±0.97 mins. and in group L is 6.26±0.92 mins. The mean duration of motor blockade for group B is 280.8±27.09 mins. and for group L is 279.0±18.10 mins. Changes in systolic diastolic and mean blood pressures along with changes in heart rate with time were depicted in (Table 2, 3).

CONCLUSIONS

From the present study, it can be concluded that intrathecal 0.5% isobaric levobupivacaine is a safe alternative to 0.5% hyperbaric bupivacaine in patients undergoing elective lower abdominal surgeries. There are no intergroup differences with respect to onset and duration of sensory blockade, maximum sensory level achieved, onset and duration of motor blockade, mean duration of analgesia, haemodynamic changes and incidence of complications. Because of less cardiotoxicity and neurotoxicity, it is concluded that levobupivacaine is an interesting and safer alternative to racemic bupivacaine.

KEYWORDS

Anaesthesia, Spinal E03.155.086.331, Anaesthesia, Epidural E03.155.086.131, Conscious Sedation E03.250.

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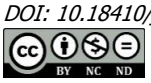


INTRODUCTION: Bupivacaine is a stereoisomer containing a racemic solution of S and R isomers. A stereoisomer is a mirror image of the same compound. Each may exert different effects. Levobupivacaine and ropivacaine, two new long-acting local anaesthetics have been developed as an alternative to bupivacaine after the evidence of its severe toxicity.[3,4] Both of these agents are pure, left isomers and due to their three-dimensional structure seem to have less toxic effects on the central nervous system and on the cardiovascular system. However, the reduced toxic potential of the two pure left isomers suggests their use in the clinical situations in which the risk of systemic toxicity related to either overdosing or unintended intravascular injection is high such as during epidural or peripheral nerve blocks. Clinically, levobupivacaine is dosed the same as bupivacaine.

So, levobupivacaine, the pure S (-) enantiomer of bupivacaine emerged as a safer alternative for regional anaesthesia than its racemic parent. It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centres in pharmacodynamic studies and a superior pharmacokinetic profile. Clinically, levobupivacaine is well tolerated in a variety of regional anaesthesia techniques both after bolus administration and continuous postoperative infusion. Reports of toxicity with levobupivacaine are scarce and occasional toxic symptoms are usually reversible with minimal treatment with no fatal outcome.

AIMS AND OBJECTIVES: The aim of my study is to compare and evaluate the efficacy of intrathecal hyperbaric bupivacaine 0.5% vs. isobaric levobupivacaine 0.5% with regard to

1. Time taken for onset of sensory blockade.
2. Maximum level of sensory blockade attained and time taken for the same.
3. Time taken for onset of motor blockade.
4. Maximum grade of motor blockade attained and time taken for the same.
5. Time taken for sensory block regression by two segments.
6. Duration of analgesia.
7. Time taken for sensory block to regress to S1.
8. Duration of motor blockade.
9. Adverse effects.

MATERIALS AND METHODS:

Study Design: The study entitled "A Randomised Controlled Double-Blind Comparative Study of 0.5% Levobupivacaine vs. 0.5% Heavy Bupivacaine for Surgeries below Umbilicus during Spinal Anaesthesia" done in the Department of Anaesthesiology at Andhra Medical College, Visakhapatnam, from November 2011 to October 2012. The surgical load of this hospital is nearly 100 surgeries per day excluding OB-GYN Department. The study was undertaken after obtaining Hospital Ethics Committee clearance as well as written informed consent from all patients after explaining and reassuring about the spinal procedure. A total of 100 patients of both sexes scheduled for elective lower abdominal surgeries under spinal anaesthesia in the age group of 18 to 55 years and belonging to American Society of Anaesthesiologists (ASA), Physical Status I and II were enrolled for the study. The enrolled patients were randomised to one of the two groups of equal-sized prospective, comparative study group using a double-blind protocol design Group B (n=50) received 3.0 mL volume of 0.5% hyperbaric bupivacaine intrathecally and Group L (n=50) received 3.0 mL volume of 0.5% isobaric levobupivacaine intrathecally. Routine preanaesthetic checkup of all the patients was done to exclude coexisting medical conditions and to assess airway and spine. Routine investigations like haemoglobin%, blood group and typing, urine examination, etc. were done.

Study Agents:

1. 0.5% Hyperbaric Bupivacaine Ampoule.
2. 0.5% Isobaric Levobupivacaine Ampoule.

Monitors: Pulse oximeter, Non-invasive blood pressure monitor by sphygmomanometer on the upper limb, ECG monitoring.

Technique: With the patient in lateral decubitus position, the skin over the back was prepared with iodine-containing sterilising solution, spirit and draped with a sterile towel. The procedure was done under full sterile precautions including gown, mask and gloves. As per protocol, the interspace chosen was L3-L4. If the attempt at this level failed, the L2-3 level was the next choice. A 23G Quincke spinal needle was introduced into the L2-L3 or L3-L4 intervertebral space gently in the midline until it reached the subarachnoid space. The position of the needle in the subarachnoid space was confirmed by dripping of cerebrospinal fluid through the needle freely. After aspirating 0.2 mL of cerebrospinal fluid into the syringe, the study drug 3.0 mL of 0.5% hyperbaric bupivacaine or 3.0 mL of 0.5% isobaric levobupivacaine was injected into the subarachnoid space slowly at the rate of 0.25 mL/sec with the bevel cephalad. The needle was withdrawn and the patient turned supine. 100% oxygen via face mask (at the rate of 4 L/mins.) was administered.

The parameters noted were onset of sensory blockade and motor blockade, maximum level of sensory blockade attained and time taken for the same noted, maximum level of motor blockade attained and the time taken for the same, two segments sensory regression time noted. Total duration of analgesia and total duration of sensory blockade and motor blockade noted.

Sensory blockade tested using pinprick method with a blunt tipped 23G needle at every minute for first 5 mins. and every 5 mins. for next 15 mins. and every 10 mins. for next 30 mins. and every 15 mins. till the end of surgery and there after every 30 mins. until sensory block is resolved.

Monitoring of Cardiac and Respiratory Parameters: Haemodynamic monitoring was done during the block every 5 mins. for first 15 mins. and every 10 mins. for next 30 mins. and once in 15 mins. till the end of surgery and postoperatively every hourly employing multi-parameter monitor, which displays Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), ECG and SpO2 hourly.

DEFINITIONS:

Onset of Sensory Blockade: Is defined as time taken from the completion of the injection of study drug till the patient does not feel the pinprick at T10 level.

Time Taken for Maximum Sensory Blockade: Is defined as the time taken from the completion of the injection of the study drug to the maximum sensory blockade attained.

Onset and Quality of Motor Blockade: Is defined as the time taken from the completion of injection of study drug till patient develops Bromage - 1.

Assessment of the Motor Blockade: Motor blockade in the lower limbs was assessed subjectively by asking the patient to move the lower limbs and was noted as follows according to the modified Bromage scale (Table 4).

Time Taken for Maximum Motor Blockade: Is defined as the time taken from the completion of the injection of the study drug to the maximum motor blockade attained.

Duration of two Segment Sensory Regression: Is defined as the time taken from the maximum level of sensory block attained till the sensation has regressed by 2 segments.

Duration of Analgesia: Is defined as the time taken from the completion of the injection of the study drug till the patient requests for rescue analgesic in the postoperative period. Assessment of degree or intensity of sensory block was done using Visual Analogue Scale Score on a 10 cm scale:

Duration of Sensory Blockade: Is defined as the time taken from the time of injection till the patient feels the sensation at S1 dermatome.

Duration of Motor Blockade: Is defined as the time taken from the time of injection till the patient attains complete motor recovery.

Hypotension: Is defined as reduction of systolic blood pressure more than 30% below baseline value and treated with increased rate of intravenous fluids and if needed injection mephentermine 3 mg increments given.

Bradycardia: Is defined as heart rate less than 60/minute and treated with injection atropine 0.6 mg IV.

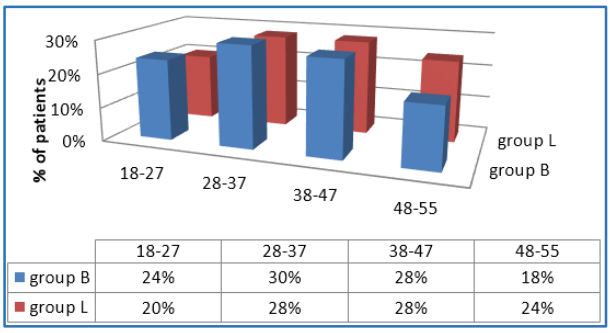
Postoperative Observations: After surgery, cardiovascular (Pulse and blood pressure) and respiratory parameters (Respiratory rate and oxygen saturation) and clinical evaluation of sensory and motor profiles were noted until the patient was transferred to the postoperative ward. Continuous monitoring and recording at regular intervals was done until the complete return of sensory and motor function. Postoperatively, the pain score was recorded by using Visual Analogue Pain Scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain), initially every 1 hr. for 2 hrs., then every 2 hrs. for the next 8 hrs. and then after every 4 hrs. till 24 hrs. Diclofenac 75 mg was given intramuscularly as rescue analgesia (RA) when VAS was >4.

Inclusion Criteria: Adult patients of either sex aged between 18 and 55 years belonging to ASA grade I and II scheduled for elective lower abdominal surgeries.

Exclusion Criteria:

1. ASA III, IV and V patients.
2. Age <18 and >55 years.
3. Pregnant females.
4. Body weight more than 100 kg.
5. Height less than 150 cm.
6. Patients using alpha-2 receptor antagonists, calcium channel blockers and Angiotensin convertase enzyme inhibitors.
7. Heart block/Dysrhythmia by ECG.
8. Contraindication to spinal anaesthesia (patient refusal, allergic to drug, coagulation disorder, infection at puncture site, increased intracranial tension and hypotension).
9. The use of any opioid or sedative in the week prior to surgery.
10. Patients with psychiatric illness and neurologic disease.

RESULTS: The minimum age in group B is 18 years and in group L if 20 years. The maximum age in both the groups is 54 and 55 years, respectively. The mean age in group B is 37.12±10.19 years and group L is 39.12±11.06 years (Fig-1).



	18-27	28-37	38-47	48-55
group B	24%	30%	28%	18%
group L	20%	28%	28%	24%

Fig. 1: Age Distribution

The mean height in Group B is 160.36±5.22 cm and in Group L is 159.38±7.86 cm. The minimum height in both groups is 150 cm and 146 cm respectively while the maximum height is 170 cm. There is no significant difference in the height of patients between the two groups (P >0.05). The mean body weight in group B is 65.40±9.41 kg and in group L is 65.42±6.43 kg. The minimum body weight in the group B is 52 kg and in group L is 54 kg. The maximum body weight in the group B is 72 kg and in group L is 80 kg. (Table 1) shows the type of surgery patients have undergone in groups.

Surgical Procedure	Groups			
	Group A		Group B	
	No. of pt's	%	No. of pt's	%
Appendicectomy	12	24%	11	22%
Inguinal hernia repair	11	22%	11	22%
TAH	4	8%	5	10%
Ovarian cystectomy	12	24%	10	20%
Ureteric procedures	11	22%	13	26%

Table 1: Type of Surgical Procedure

There is no significant difference in the type of surgical procedure in patients between the groups (P>0.05). The mean time of onset of sensory blockade in group B is 1.78±0.708 mins., in group L is 2.5±0.863 mins. There is no clinical significance between group B and L regarding mean time for onset of sensory blockade. Five out of 50 in group B, twelve out of 50 in group L attained level T_4 of sensory blockade. Nineteen out of 50 in group B and fourteen out of 50 in group L attained T_6. Nineteen out of 50 and seventeen out of 50 attained level T_8. Five out of 50 and seven out of 50 attained T_9 level of sensory blockade.

Two out of 50 in group B and none from group L attained T_{10} level of sensory blockade. The mean time taken for attaining maximum sensory blockade is 8.98±1.477 mins. in Group B and 8.08±1.70 mins. in group L. There is no clinical significant difference between group B and L regarding the mean time for attaining maximum sensory blockade. The mean time taken for regression of sensory blockade by two segments is 86.3±6.22 mins. in group B and 86.0±6.08 mins. in group L. The mean duration of analgesia for group B is 161.0±12.66 mins. and group L is 164.20±9.55 mins. The mean duration of sensory regression to S_1 in group B is 201.2±12.59 mins. and in group L is 200.7±12.25 mins. The mean time taken for the onset of motor blockade is 1.98±0.55 mins. in group B and in group L is 2.08±0.70 mins. The mean time taken for attaining maximum motor blockade in group B is 6.56±0.97 mins. and in group L is 6.26±0.92 mins. The mean duration of motor blockade for group B is 280.8±27.09 mins. and for group L is 279.0±18.10 mins. Changes in systolic, diastolic and mean blood pressures along with changes in heart rate with time were depicted in (Table 2, 3).

Weight in Kgs.	Groups	
	Group A	Group B
n	50	50
Mean	65.40	65.42
ST Deviation	9.41	6.43
Min. Weight	52	54
Max. Weight	72	80
T-Value	-0.01241	
P-Value	0.50	

Table 2: Body Weight Distribution

Time Taken for Sensory Onset in Mins.	Groups	
	Group B	Group L
Mean	1.78	2.5
ST Deviation	0.708	0.863
Minimum	1	1
Maximum	3	4
P-Value	0.175221	

Table 3: Mean Time Taken for Sensory Block Onset in Minutes

Bromage 0 - Patient is Able to Move the Hip, Knee and Ankle.
Bromage 1 - Patient is Unable to Move the Hip, But is Able to Move the Knee and Ankle.
Bromage 2 - Patient is Unable to Move the Hip and Knee, But is Able to Move the Ankle.
Bromage 3 - Patient is Unable to Move the Hip, Knee and Ankle.

Table 4: Bromage Scale

In the group B (bupivacaine group), we observed a fall in mean SBP, which is maximum of 12.22 mmHg from mean basal SBP at 5th mins. and 10th mins. (10.01% fall from basal SBP) and in group L (levobupivacaine) a fall in mean SBP, which is maximum of 13.81 mmHg from mean basal SBP at 5th and 10th mins (10.54% fall from basal SBP). The fall in SBP from basal to 10th minute recording is statistically not significant between group B and group L and also thereafter there was no significant difference observed in the mean SBP between the two groups. No significant difference was observed in basal mean SBP and mean SBP at 180 mins. between the two groups (Fig. 2).

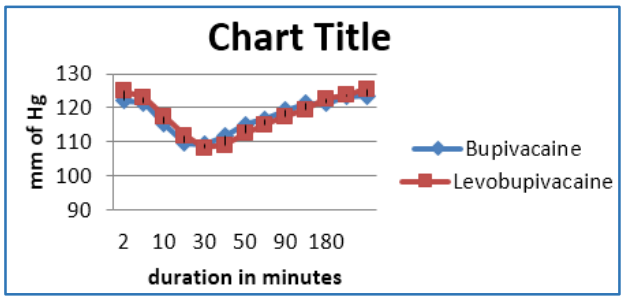


Fig. 2: Mean SBP in mmHg at Various Intervals

We observed a fall in mean DBP, which is maximum of 10 mmHg from mean basal DBP at 5th and 10th mins. (13.19% fall from basal DBP) with group B and in group L a fall in mean DBP, which is maximum of 9.52 mmHg from mean basal DBP at 5th and 10th mins. (12.79% fall from basal DBP) (Fig - 3).

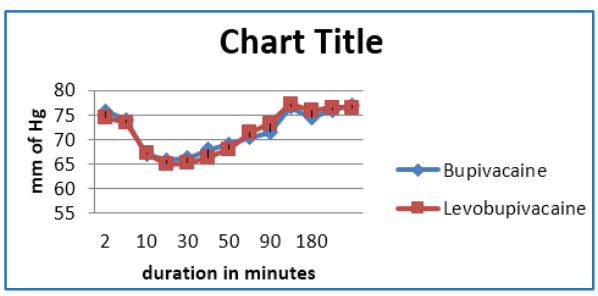


Fig. 3: Mean DBP at Various Time Intervals in mmHg

It was observed that a fall in mean MAP, which was 11.28 mmHg from mean basal MAP at 10th mins. in group B (14.03% fall from basal MAP) and in group L (levobupivacaine) a fall in mean MAP, which was 11.78 mmHg from mean basal MAP at 10th mins. (13.02% fall from basal MAP). SPo2 remained stable throughout the observation period (Fig - 4).

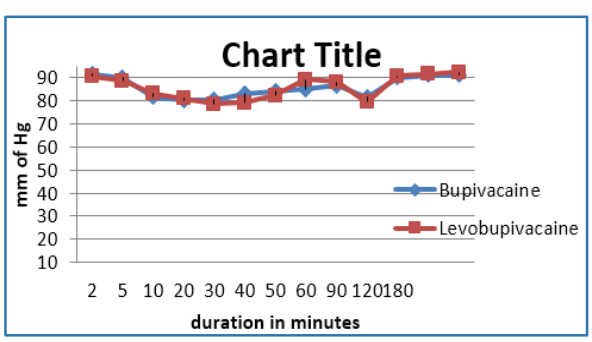


Fig. 4: Mean MAP at Various Time Intervals in mmHg

None of the patients with sufficient spinal anaesthesia required supplemental oxygen. Haemodynamic and respiratory variables remained stable from skin incision throughout the surgical procedure. No patient required blood replacement. Three out of 50 and in Group B and none out of 50 patients in Group L developed hypotension, which was statistically significant (p >0.05). All the patients who developed hypotension were treated with intravenous fluids and vasopressor. Five out of 50 in Group B and none out of 50 patients in Group L developed bradycardia, which was statistically significant (p >0.05). The temporal events were summarised in (Table 5, 6) in both comparative groups.

Group vs. Bradycardia	Absent	Present	Total
Bupivacaine	45 (90%)	5 (10%)	50 (100%)
Levobupivacaine	50 (100%)	0	50 (100%)
Total	**95 (95%)**	**5 (5%)**	**100 (100%)**

Table 5: Incidence of Bradycardia

Group vs. Hypotension	Absent	Present	Total
Bupivacaine	47 (94%)	3 (6%)	50 (100%)
Levobupivacaine	50 (100%)	0	50 (100%)
Total	**97 (97%)**	**3 (3%)**	**100 (100%)**

Table 6: Incidence of Hypotension

DISCUSSION: Glaser et al reported surgical sensory and motor block of similar characteristics and recovery over equal dose ranges of levobupivacaine and bupivacaine. It was demonstrated in healthy volunteers and confirmed in surgical patients. The regression of motor block was significantly more rapid after levobupivacaine and ropivacaine than bupivacaine, which may be advantageous for early ambulation after daycare surgery. According to the study conducted by Glaser C, Marhofer P et al, intergroup differences between levobupivacaine and bupivacaine were insignificant both with regard to the onset time and the duration of sensory and motor blockade (11±6 versus 13±8 mins.; 10±7 versus 9±7 mins.; 228±77 versus 237±88 mins.; 280±84 versus 284±80 mins.).[5] Our study is also consistent with the studies conducted by Opas Vanna MD et al who observed when levobupivacaine and bupivacaine compared in Spinal Anaesthesia for Transurethral Endoscopic Surgery that the peak block height of the levobupivacaine group was T4 in the bupivacaine group was T6 and average in both groups were T9.

No statistically significant difference was seen in the onset of sensory, motor blockade and the duration of complete motor blockade.[6] Sari R.; Dursun M.; Pirat A.; Dogan R in their study of levobupivacaine versus racemic bupivacaine in percutaneous nephrolithotomy with spinal anaesthesia, which concluded that there were no significant differences in sensory block regression time between the two groups (p >0.05).[7] The duration of analgesia in our study correlated with the study done by Glaser, Christian MD, Marhofer, Peter MD namely Levobupivacaine Versus Racemic Bupivacaine for Spinal Anaesthesia, which concluded that there was no significant difference in first VAS scores at the PACU (2.6±1.5 in the Levobupivacaine versus 3.4±2.4 in the Bupivacaine group).[5] Carpenter et al showed that peak height of block was the main variable for bradycardia and hypotension during spinal anaesthesia, the similar intergroup haemodynamics in our study were

consistent with the fact that both study groups showed a mean peak block height of T8.

CONCLUSION: From the present study, it can be concluded that intrathecal 0.5% isobaric Levobupivacaine is a safe alternative to 0.5% hyperbaric Bupivacaine, in patients undergoing elective lower abdominal surgeries. There are no intergroup differences with respect to onset and duration of sensory blockade, maximum sensory level achieved, onset and duration of motor blockade, mean duration of analgesia, haemodynamic changes and incidence of complications.

Because of less cardiotoxicity and neurotoxicity, it is concluded that Levobupivacaine is an interesting and safer alternative to Racemic Bupivacaine.

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