Comparison of Epidural Levo Bupivacaine (0.5%) with Racemic Bupivacaine (0.5%) for Lower Abdominal Surgery

Reshma Sugathan[1], Anu Antony[2]

ABSTRACT

Introduction: Levobupivacaine, the pure S (-) isomer of bupivacaine, is attributed to have less cardiotoxicity when compared to racemic bupivacaine. Levobupivacaine increase the margin of safety for epidural anaesthesia. Study aimed to investigate the clinical efficacy of levoupivacaine compared with racemic bupivacaine for epidural anaesthesia.

Material and Methods: We conducted an observational multicentric study comparing sensory and motor block produced by 0.5% levobupivacaine (17 ml, 85 mg) with that of 0.5% racemic bupivacaine in 60 patients undergoing elective lower abdominal surgery under epidural anaesthesia.

Result: No statistically significant difference was found between the groups in terms of sensory and motor blockade. The time to onset of adequate sensory block (T10dermatome) was similar in both treatment groups (6.20+/-2.23 min for levobupivacaine and 6.17+/-2.61 min for bupivacaine). Average peak block height reached was T4 for both group. Time for sensory block to reach T6 level was comparable. (10.97+/-2.89 for bupivacaine and 11.23 +/-5.99 for levobupivacaine.) Time for regression of sensory block to T10 level was similar (224.17+/-30 for bupivacaine and 224.83 +/-23 for levobupivacaine). There was no difference in the onset and intensity of motor block between two groups.

Conclusion: 0.5% levobupivacaine and 0.5% bupivacaine produced effective epidural anaesthesia and their effects were clinically indistinguishable. Levobupivacaine could be a good alternative to bupivacaine in patients administered epidural anaesthesia.

Keywords: Epidural Anaesthesia, Bupivacaine, Levobupivacaine

INTRODUCTION

Epidural anesthesia is a regional anesthesia technique which is extensively used, especially in surgeries involving the abdomen and lower extremity. Its potential to decrease postoperative morbidity and mortality has been demonstrated by numerous studies.[1]

The epidural space is bounded superiorly by the fusion of the spinal and periosteal layers of the duramater at the foramen magnum. Inferiorly, it is bound by the sacrococcygeal membrane.

Anterior boundary is formed by the posterior longitudinal ligament, vertebral bodies and discs while the pedicles and intervertebral foraminae form the lateral boundary. The ligamentum flavum, capsule of facet joints and the laminae form the posterior boundary of the epidural space.[2]

The contents of the space is constituted by semi-liquid fat, lymphatics, arteries, loose areolar connective tissue, the spinal nerve roots, and extensive plexus of veins.[2] Epidural anaesthesia is instituted by the injection of drugs through a catheter placed into the epidural space. The injection can result in blocking the transmission of signals through nerve fibers in or near the spinal cord.Three modes of delivery of local anaesthetic can be used;1) continous infusion 2) PCEA patient controlled extradural analgesia 3) intermittent bolus.[3] A person receiving an epidural may receive local anaesthetic, an opioid, or both. Lidocaine, mepivacaine, bupivacaine, ropivacaine, and chloroprocaine are the usually used local anaesthetics.[4] Common opioids include morphine, fentanyl, sufentanil, buprenorphine, tramadol and pethidine.[4]

Racemic bupivacine has been widely used as a local anaesthetic because of its long duration of action and beneficial ratio of sensory to motor block when used for epidural analgesia. However, there have been reports of death attributable to bupivacine induced cardiotoxicity in patients after accidental intravascular injection.[5] Cardiac toxicity can occur after accidental intravascular injection of bupivacaine. Bupivacaine has high affinity for the myocardial Na+ channel. A significantly increased P-R interval and QRS duration was found for R(+) bupivacaine compared with S (-) bupivacaine. Also, a reduced recovery from complete AV block was found for R (+) bupivacaine compared with S (-) bupivacaine. Lack of total recovery from cardiotoxicity is one of the most important disadvantages of racemic bupivacaine in comparison of other amide-type local anaesthetics.[6]

This is a major drawback; although the incidence of death is small, the concern is sufficient that the Food and Drug Administration currently prohibits the use of 0.75% bupivacine in obstetrics and the use of bupivacine in IV regional anaesthesia. Despite evidence showing improved operating condition, in nonobstetrics abdominal surgery and lower extremity surgery, many practitioners have discontinued its use.

In recent years levobupivacaine, the pure S (−)-enantiomer of bupivacaine,emerged as a safer alternative for regional

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anesthesia than its racemic parent.[7] It possesses reduced affinity to myocardial and central nervous vital centers.

The affinity of the S (-) isomer to the cardiac sodium channel in the inactive state is lower than that of the R (+) isomer.[8] Reports of toxicity with levobupivacaine are scarce and occasional toxic symptoms are usually reversible with minimal treatment with no fata outcome.[8] Yet, levobupivacaine has not entirely replaced bupivacaine in clinical practice.Theoretically levobupivacaine and bupivacaine produce equal surgical anaesthesia and equal labor pain control with comparable maternal and fetal outcome but of late, the equipotency of the two drugs has come under scrutiny, prompting clinicians to enhance the levobupivacaine dose in an attempt to ensure adequate surgical anesthesia.

We compared the clinical efficacy of 0.5% levobupivacine with that of 0.5% bupivacine in patients undergoing elective lower adominal surgery with epidural anaesthesia.

MATERIAL AND METHODS

This was an observational multi centric study done across various hospitals in south Kerala.

Study period was between 10-10-2017 to 10-10-2018. After institutional review board clearance 60 ASA grade I&II patients who fulfilled the inclusion and exclusion criteria, as given below were recruited to the study. They were randomly allocated to two groups of 30 each.

Randomization was by block envelope randomization method. Sample size was calculated using the formula

$$n=2\left[\frac{(Z_{\alpha}-Z_{1-\beta})\sigma}{d}\right]^{2}$$

1-β = power of study

Z = 1.96 for α at 5% level of significant

σ = mean

d = absolute precision

Group 1 -Patients receiving 0.5% epidural racemic bupivacaine

Group II -Patients receiving 0.5% epidural levobupivacaine

Patients of ASA grade I and II aged between 18 to 60 years, having a height of 150 to 170 cm and posted for elective lower abdominal surgeries were included in the study. Exclusion criteria include patient refusal, having cardio pulmonary illness, patients with neurological disorders, history of hypersensitivity reaction to any of the study medication, Bleeding disorders and patient on anticoagulants and infection at site of puncture.

After pre anaesthesia check up, written informed consent was taken.

Intravenous line with Ringer's Lactate was initially started. Standard monitoring of vital signs was instituted, that included non invasive blood pressure, ECG, respiratory rate, heart rate, pulse oximetry.

All patients were pre loaded with 10 ml / kg of lactated Ringers solution over 10- 15 mts before induction of the allocated anesthetic technique. All patients were pre medicated with midazolam 0.03mg /kg. The epidural anaesthesia was performed with the patient in right lateral position at L2 - L3 or L3- L4 inter space, about half an hour prior to surgery. Lignocaine 1% was used to infiltrate the skin and subcutaneous tissues in the above space. Epidural space identified with 18 guage Tuohy needle by loss of resistance to air. Epidural space confirmed by giving test dose with 2% lignocaine 3ml and 1 in 2 lakh adrenaline. When there was no evidence of intravascular or subarachnoid injection 17 ml of study solution (0.5% levobupivacaine or 0.5% racemic bupivacaine) were administered incrementally over a 5 minute period. Total volume of study drug administerd was 17 ml, providing a total dose of 85 mg. All patients were administered oxygen 5 litre/minute through ventimask.

Absence of pain from a pin prick at the T10 (umbilicus) level was recorded as the onset time of sensory block. Adequate block to initiate surgery was defined as sensory block bilaterally to dermatome T6. The time taken to achieve this level of anaesthesia was the primary efficacy measure. Secondary measures include – onset time of sensory block, peak block height, time to reach peak block, total duration for regression to T10 level. Sensory block was measured by pinprick induced with 26 guage hypodermic needle at 0,2,5,10,15,20,25,30, and 60 minutes post injection and every 30 min thereafter until regression of sensory block to T 10 level was observed.

The degree, and duration of motor block to reach maximum level were measured in both legs by using a modified Bromage scale. Motor block was measured at 0,5, 10, 15,20,25 and 30 min post dose and every 30 min thereafter.

Hemodynamic variables – Mean arterial pressure, heart rate were recorded at baseline (Pre injection), at the end of injection of epidural solution (T1) at 5 (T2), 10 (T3), 20 (T4), 30 (T5) and 60 (T6) minute after the injection.

A decrease in systolic blood pressure of at least 30% and was treated with IV fluids and/or vasopressor. Patients were stabilized with 0.6mg of atropine when their heart rate dropped under 50 beats /min. Duration of surgical procedures was in the range of 1.5 to 2 hours.

RESULTS

The two groups were similar in terms of demography, ASA grades and duration of surgery.

Baseline pulse rate, systolic blood pressure, diastolic blood pressure were comparable,as *P*- values are > 0.05.

Mean time for onset of sensory block was 6.17 minutes for group I and 6.2 minutes for group II. Both drugs were similar with respect to the onset of sensory block, as *P*-value is >0.05 (Table-I).

Group 1 took about 10.97 minutes to reach T6 level, whereas group II took 11.23 minutes for the same. No significant difference between two groups with respect to time taken for both drugs to reach T6 level, as *P*- value is more than 0.05.

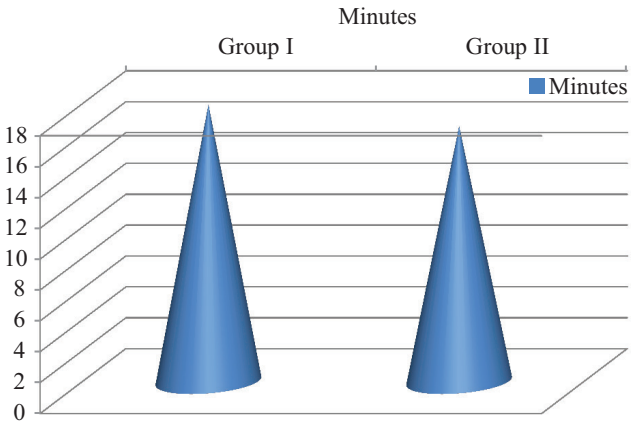
Majority of patients in both groups attained T4 level. In group1, 3% of patients attained T2 level and 9% attained T3 level. In group II no patients attained T2 level and only 7% of patients attained T3 level. No statistical significance as

	Group	N	Mean	Standard deviation	t	P-value
Sensory block onset(min)	I	30	6.17	2.614	0.053	0.958
	II	30	6.20	2.235		

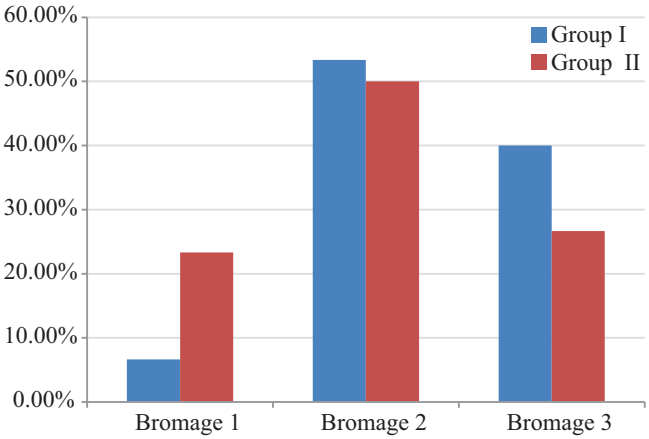
Table-1: Comparison of Time Taken For Onset of Sensory Block

	Group	N	Mean	Standard deviation	t	*P*-value
Regression to T10 (Minutes)	Group I	30	224.17	30.402	0.095	0.925
	Group II	30	224.83	23.507		

Table-2: Comparison of time taken for regression of sensory block to T10



Graph-1: Comparison of time taken for maximal cephalic spread (TMCS) of sensory block



Graph-2: Comparison of time taken for regression of sensory block to T10

P- value >0.05.

Group 1 took 17.93 minutes for maximal cephalad spread group II took 16.53 minutes. The two groups were comparable statistically. (*P*- value >0.05). (Graph-I)

Group I took 224.17 minutes and group 2 took 224.83 minutes for regression to T10 level. Not statistically significant as *P* -value is > 0.05.(TABLE: II)

Majority of patients in both group attained Bromage scale (53.33% in group I and 50% in group II).40% of patients in group 1 attained bromage scale 3 blockade, whereas it was only 26.66% for group II. No statistical significance as *P*-value is >0.05. (Graph II)

Time taken for maximal motor block was comparable as *P*-value was >0.05. Mean time taken to reach bromage scale 1 in Group I (N=2) and Group II (N=7) was 30minutes. Time taken to attain Bromage scale 2 in Group I (N=16) and Group II (N=17) were 30 and 35 minutes respectively. Time taken to attain Bromage scale 3 in Group I (N=12) and Group II (N=8) were 29.58 and 28.13 minutes repectively.

Changes in mean arterial pressure were comparable between the two groups.*P* –value>0.05. Changes in heart rate, after drug administration, of both groups were comparable, as *P*-values were more than 0.05.

The two groups were comparable in terms of occurrence of adverse effects like hypotension and bradycardia. 5 patients in Group I and 4 patients in Group II had hypotension (*P*>0.05). Three patients in Group I and one patient in group II developed bradycardia. (*P*>0.05).

DISCUSSION

Advantages of epidural anesthesia include conscious state of the patient, early awareness of complications owing to the ongoing cooperation with the patient, intact airway reflexes, less stress response, less thromboembolism, provision for post-operative analgesia compared to general anesthesia, and less motor blocks, while disadvantages are late onset of its effects and possible development of motor block.[9]

Epidural anesthesia followed by epidural postoperative analgesia is also preferred for high-risk cardiac patients.[10] Bupivacaine is a long-acting local anesthetic from the amino-amide subgroup, which is frequently used for local infiltration and epidural and spinal anesthesia. Though it has been safely used in regional anaesthesia, fatal cardiotoxicity has been reported following accidental intravascular injection.[11,12] An important cause of cardiovascular side effects is bupivacaine leaving sodium channels slowly.[13] Therefore, local anesthetics with similar actions to bupivacaine, but there is a need for dugs with reduced effects on the cardiovascular system.

Levobupivacaine is a pure S (-) enantiomer with reduced affinity to the cardiac sodium channel in the inactive state than the R (+) isomer.[13] In the studies conducted, levobupivacaine has been demonstrated to present similar pharmacokinetic characteristics to bupivacaine and to be less cardiotoxic and neurotoxic.[14] Levobupivacaine is considered a good alternative to bupivacaine, due to its reduced adverse effects on the cardiovascular system.

In our study, 85 mg each of 0.5% isobaric bupivacaine and 0.5% isobaric levobupivacaine were compared in 2 groups of 30 patients who underwent elective lower abdominal surgery, in terms of anesthetic and hemodynamic parameters. In our study, time to onset of adequate sensory

block (T 10dermatome) was similar in both treatment groups (6.20+/-2.23 min for levobupivacaine and 6.17+/-2.61 min for bupivacaine). There was no statistically significant difference between the times to reach the sensory block sufficient for the surgical intervention, that is T6 level (10.97 min in bupivacaine group and 11.23 min in levobupivacaine group).

Average peak block height reached was T4 for both group. Though not statistically significant, bupivacaine showed a higher cephalic spread of sensory block. Time for regression of sensory block to T10 level was similar (224.17+/-30 for bupivacaine and 224.83 +/- 23 for levobupivacaine). Cox et al found that 0.5% and 0.75% levobupivacaine, administered for epidural anesthesia, was tolerated by patients as well as bupivacaine was, and there was not a significant difference in onset time, maximum spread of sensory block.[15] They reported that duration sensory block was 32 and 45 min longer with levobupivacaine (0.5% and 0.75% respectively) compared to equal doses of bupivacaine.[15] In our study duration of sensory block was similar in both groups.

Kopacz and Allen reported that sensory block onset time of levobupivacaine was similar to the onset time of 0.5% bupivacaine.[16] Peak block height attained was also similar. Time to complete regression of sensory block was significantly longer with levobupivacaine than bupivacaine. In our study regression of sensory block to T10 was similar in both groups.

Kara et al reported that, there is no significant difference between these two drugs in terms of onset and regression times of sensory block, time for sensory block to reach T6, and for initial analgesic requirement time.[16] These results are consistent with our study results.

There was no significant difference in grade of motor block between two groups. Majority of patients in both group attained Bromage scale 2(53.33% in bupivacaine group and 50% in levobupivacaine group) However number of patients attaining Bromage scale 3 was more for bupivacaine group (40% for bupivacaine group and 26.66% for levobupivacaine group). But this was not statistically significant as p value was >0.05.

Time of motor block to reach maximum level was comparable between two groups.

Kopacz and Allen found in the patients to which they administered epidural bupivacaine and levobupivacaine that onset of motor block was about 1 min shorter in the group that received levobupivacaine. They reported that extremity block occurred within 30 min in only 14% of the patients that received levobupivacaine, compared to 71% of the patients that received bupivacaine.[16] This was similar to our study. In our study, the patients in both groups who had Bromage scale 3 motor block had onset time shorter than others. That is patients who developed intense motor block had shorter onset time by 1-2 minutes.

Cox et al reported there was no significant difference in onset time or grade of motor block between racemic and levobupivacaine.[15] This was similar to our findings.

There was no statistically significant difference between two groups in systolic blood pressure and heart rate. Hypotension was observed in 5 patients in bupivacaine group and for 4 patients in levobupivacaine group. Incidence of bradycardia was 3 and 1 for bupivacaine and levobupivacaine respectively. All patients responded to treatment described. Other side effects like nausea, vomiting, need for supplemental analgesia and anaesthesia was nil in both groups.

Cox et al, Bader et al[18] and Kopacz and Allen evaluated mean arterial pressure, heart rate and oxygen saturation and did not find a significant difference between the two groups. Their results are consistent with our study results.

No toxicity signs were found in any patient. This could be due to the fact that patients were selected from low-risk groups, and the doses were not at high limits.

Finally, we concluded from this study that there was no difference between 0.5% bupivacine and 0.5% levobupivacine in patients receiving epidural anaesthesia for lower abdominal surgeries, with respect to onset of sensory and motor block, time to achieve surgical anaesthesia, regression of sensory block or quality of sensory and motor block.

There were no significant side effects or signs of local anaesthetic toxicity in both groups.

So in clinically effective doses both racemic bupivacaine and levobupivacaine provides adequate anaesthesia, without side effects or complications. So both can be used in patients, provided dose and compounding factors are taken care of.

CONCLUSION

On the basis of the study following conclusions were drawn:

1. Onset of sensory block was same for levobupivacaine and bupivacaine.
2. Time taken for sensory block to reach T6 dermatomal level was same.
3. Maximum cephalad spread of sensory block were comparable. Though not statistically significant, bupivacine showed a tendency for higher cephalic spread.
4. Time taken for regression of sensory block to T10 level was similar in both groups.
5. Levobupivacine shows a trend, although not statistically significant, towards less motor blockade.
6. No significant differences between two groups in terms of arterial pressure or heart rate.

We finally concluded that levobupivacine, the pure S (-) enantiomer of racemic bupivacine is an effective local anaesthetic drug for epidural anaesthesia, in lower abdominal surgeries and is comparable to racemic bupivacine. Reduced toxicity of levobupivacine was, therefore, not at the expense of a decrease in clinical efficacy.

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