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Comparative evaluation of the clinical efficacy of 0.5% levobupivacaine and 0.5% racemic bupivacaine in epidural anaesthesia for elective varicose vein surgery

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Abstract

Background and Aim: Racemic bupivacaine is known to be the most cardio toxic among the amide local anaesthetic. In search of an alternative it was found that the levo enantiomer has a better safety profile. This purpose of this study is to compare the clinical efficacy of 0.5% levobupivacaine with 0.5% racemic bupivacaine in epidural anaesthesia.

Materials and Methods: After the institutional ethical committee approval this double blind randomized prospective study was conducted on 50 male patients between January and August 2011. 25 patients were allocated to each group; group L received levobupivacaine and group R received racemic bupivacaine. Onset time, duration of block, level of sensory block and motor block were assessed and compared.

Observation and Results: The mean onset time was 7.739±3.3033 and 8.04±3.048 minutes in group L and in group R respectively. Level of sensory block level noted was between T10 to T5, but most patients had the level at T6. The mean duration of residual analgesia was 412.56 ± 39.11 minutes in L group and 409.56 ± 44.46 minutes in R group. The onset time, duration of block, level of sensory block were comparable and were not statistically significant. But the motor block was found to be intense and was statistically significant in the patients in R group (p 0.0498) than in L group.

Conclusion: In comparison to racemic bupivacaine, levobupivacaine produces a differential blockade but onset, duration, level of sensory blocks was similar. However racemic bupivacaine produces intense motor blockade when compared with levobupivacaine.

Keywords: Chirality, Racemic bupivacaine, Levobupivacaine, Epidural, Bromage scale, Differential block.

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Introduction

Chirality is a Greek word which means hand. Stereoisomers are molecules that have identical atomic and chemical properties with different spatial arrangement of their atoms and they cannot be superimposed on one another. A pair of such a stereo isomer is termed as enantiomers and each will rotate the plane polarized light in a magnitude that is equal but in opposite directions. Compound that rotate plane polarized light clockwise is `R' isomer from Latin Rectus (right) and when a compound moves the plane polarized light anti-clockwise it is called `S' isomer from Latin Sinister (left). When these isomers are present in equal molar amounts in a compound it is called as a racemic or racemate mixture. Enantiomers have identical physical and chemical properties so they will have similar pKa and lipid solubility.[1,2]

Bupivacaine is widely used local anaesthetic and is a mixture of dextro and levo enantiomers and it is also cardiotoxic.[1,2] Toxic effects of bupivacaine were first described by Aberg and colleagues in 1972.[1,2,3,4] It was discovered that the R form of the drug is much more toxic than the S enantiomer.[2,3] Once this was recognized the search to isolate an alternative less toxic long acting anaesthetic was made and developed – Levobupivacaine the S enantiomer.[2,3,4,5]

The present study was conducted to compare the onset time, duration of analgesia, sensory and motor block of 0.5% levobupivacaine and 0.5% racemic bupivacaine on randomly allocated 50 male patients.

Materials and Methods

After the institutional ethical committee approval 50 male patients in the age group of 20 to 50 years who were to undergo elective varicose vein surgery between January and August 2011 were chosen for this double blind randomized prospective study. Patients involved were given a detailed explanation about the study and an explained informed consent was obtained. Anaesthesiologist who allotted the local anaesthetic samples was not involved in this study. Therefore the observer was not aware of the type of local anaesthetic in each presentation.

Inclusion Criteria

- ASA physical class I or II scheduled for varicose vein surgery
- Weight between 45 – 65 Kilograms

Exclusion Criteria

- ASA physical class III or more
- Patient refusal
- Patients with coagulation disorders
- Patients with systemic illness such as cardiac, respiratory and neurologic disorders etc.
- Allergy to local Anaesthetics
- Local infection at the site of injection

All patients included in the study were evaluated as per institutional protocol with full blood count including hemoglobin & platelets and also blood grouping, urea, creatinine, electrolytes, blood sugar, coagulation profile, chest X-Ray, Electrocardiography and urine analysis for albumin, sugar. Heart rate, Blood pressure, respiratory rate, SpO2 in room air and weight were noted down. They were explained about the visual analogue scale during the preoperative visit.

Patients were premedicated with injections Midazolam 2mg I.V, Ranitidine 50 mgs I.V and Ondansetron 4mgs I.V one hour before the procedure. Once shifted to operating room, 5 lead Electrocardiogram, pluseoxymetry and noninvasive blood pressure monitoring were connected.

Base line heart rate, oxygen saturation and blood pressure were noted down. Venous access with 18G cannula was secured in the opposite side to the procedural limb. Preloading was done with a liter of Ringers lactate solution. The patient was made to lie down in a left lateral position. Skin painted with antiseptic solution and draping was done. The intervertebral space corresponding to the tuffier`s line (intercristal line) was identified, skin and subcutaneous tissue infiltrated with 2ml of 2% lidoocaine. Using 18G Tuhoy needle epidural space was identified with loss of resistant technique using air. Test dose with 3 ml of 2% lidocaine with adrenaline (1:200,000) was given and the absence of intravascular or intrathecal placement ruled out. 20 ml of the sample solution was injected through Tuhoy needle.

Patient was then turned supine and following observations were made accordingly. Heart rate, blood pressure, respiratory rate and oxygen saturation every 2 minutes for the first 10 minutes and every 5 minutes afterwards till the end of the procedure. Grouping was done on the first postoperative day.

Anaesthesia related parameters like

Onset time which was taken as the time between end of epidural injection and loss of perception of cold at dermatome level T_{10}.

Upper sensory block as that of the highest level of absence of pin prick at the end of 30 minutes after the epidural injection.

Duration of surgical analgesia was observed as the onset of analgesia to the visual analogue score of 5 and

Motor block was assessed using Bromage scale one hour after the epidural injection.[7,8,9]

Adverse effects was checked by the observer in the operating room and recovery room

- Pain at the injection site
- Shivering
- Nausea and vomiting
- Bradycardia
- Hypotension - drop of more than 30% of baseline[6]
- Hypoxia - SpO2 less than 90% were recorded in operating as well as recovery room.

Data entry was done in Microsoft office Excel 2010. Student `t' test were used for statistical comparison between measurements and chi-square test for nonparametric data using IBM SPSS15 statistical software. The P value of < 0.05 is considered significant.

Observation and Results

The distribution of age (Table 1), weight (Table 2) and sex of the patients in both the groups were similar and comparable. The mean heart rate (Table 3), Mean Arterial pressure (Table 4), Respiratory Rate (Table 5) and duration of surgery rate and oxygen saturation between the two groups were comparable and did not have any significant difference. Throughout the intra and postoperative period the mean arterial pressure was also statistically similar.

Table 1: Distribution of Age

Age(yrs.)	Mean	Standard Deviation	t-value/chi-square	P value
Levo	36.08	7.34	0.7280	0.4703
Racemic	35.17	8.13		

Table 2: Distribution of Weight

Weight (Kg)	Mean	Standard Deviation	t-value/chi-square	P value
Levo	57.26	4.02	0.8101	0.4220
Racemic	56.24	4.65		

Table 3: Distribution of Heart Rate

Heart Rate (Beats/Min)	Mean	Standard Deviation	t-value/chi-square	P value
Levo	83.04	5.08	0.5730	0.5695
Racemic	82.16	5.56		

Table 4: Distribution of Mean Arterial Pressure

Mean Arterial Pressure	Mean	Standard Deviation	t-value/chi-square	P value
Levo	94.96	4.04	0.3904	0.6981
Racemic	95.36	3.09		

Table 5: Distribution of Respiratory rate

Respiratory Rate (Rate/min)	Levobupivacaine	Racemic Bupivacaine	Total
15	3	7	10
16	11	14	25
17	6	3	9
18	3	1	4
Total	23	25	48

When observed that the range of onset of action for L group was 4.5 minute to 13 min with a mean onset time of 7.739±3.3033 min and for R group the onset was 5 min to 13.5 min with a mean onset time of 8.04±3.048 min. The mean onsets of action in both the

groups were statistically insignificant as shown in the Table below.

Table 6: Onset of action

Onset of action(T_{10}) (Minutes)	Levobupivacaine	Bupivacaine	Total
4	1	1	2
5	6	5	11
6	3	4	7
7	5	5	10
9	2	2	4
10	1	2	3
11	1	2	3
12	1	1	2
13	2	1	3
14	1	2	3
Total	23	25	48

Highest levels of sensory blockade that was attained in both the group were till T5 dermatome. Most patients had their level at T6. Upper sensory block level was comparable and showed no significant statistical difference. Analgesia was adequate to perform varicose vein surgery in all the patients with no need of supplemental analgesia.

Table 7: Height of block

Level of Sensory Block	Levobupivacaine	Bupivacaine	Total
T_5	2	3	5
T_6	6	8	14
T_7	4	4	8
T_8	5	4	9
T_9	4	1	5
T_{10}	2	5	7
Total	23	25	48

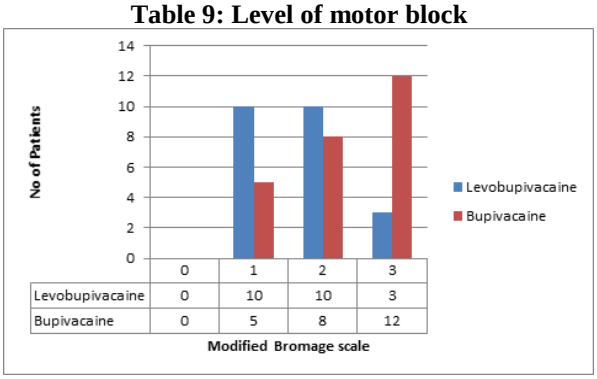
The intensity of motor block was assessed by modified Bromage scale.[7, 8,9,10]

Table 8: The description of modified Bromage scale

Modified Bromage Scale	Observation
0	Free movement of leg and feet
1	Inability to raise leg but moves knee and feet
2	Inability to flex knees but move feet
3	Unable to move knee and feet

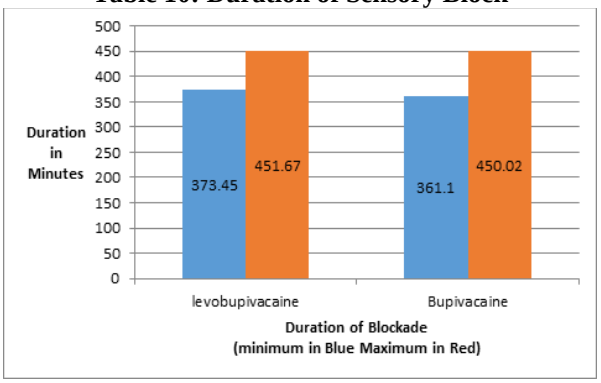
The level of motor blockade assessed at the first hour is shown in the Table 9.

Table 9: Level of motor block



Motor block is found to be significantly different in both the groups with the p value of 0.0498. Intensity of the motor block was higher in Bromage scale in the R group compared to L group.

Table 10: Duration of Sensory Block



The duration of the sensory block was assessed using the visual analogue scale measuring one to ten. A score of 5 was taken as the end of duration of the sensory block as the patient was given analgesics. The duration was similar in both the groups with a mean duration of residual analgesia of 412.56 ± 39.11 minutes in L group and 409.56 ± 44.46 in R group.

Discussion

The risk of cardiovascular toxicity of bupivacaine is well known and is the cause of high mortality and morbidity due to vascular absorption. This lead the research and development of newer local anaesthetic with a better safety profile. It was found that the presence of chiralic or asymmetric carbon in some local anaesthetic amide amines changes the resolution of enantiomers with different pharmacologic profiles. Dextro bupivacaine had a higher cardiac depressive characteristic than the levo form or the dextro form. Studies had shown encouraging results as a function of chirality, especially after it was known that the levo isomer was less cardio toxic than the racemic or dextro isomer.[1,2,3,4] The lower systemic toxicity could also be due to the intrinsic vasoconstrictor effect of the levo form which reduces the absorption.[2,3,5]

In our study the mean duration of surgery was uniform in both the groups. The mean duration and the quality of analgesia were adequate in both the groups. None of the patients needed additional perioperative analgesia.

The mean duration in onset of analgesia was similar in both the groups, levo group being 7.739±3.033 and 8.040±3.048 minutes. The results were comparable and had showed no statistical significance.[3,4,7,8,9,11,12]

The duration of sensory block was also similar in both with a mean duration in residual analgesia of 412.56±39.11 minutes in levo group and 409.56±44.46 minutes in racemic group which was similar to the studies done by Bader AM et al[3] Bay Nielsen et al.[5] It was contrasting to the study by Cox CR et al;[8] Kopacz DJ et al[10] who claimed that the duration of sensory block was significantly longer with levobupivacaine than racemic bupivacaine.

The most important difference between the groups was in degree and quality of the motor blockade. The greater muscle relaxation (modified Bromage scale 3) was observed in racemic bupivacaine than with levobupivacaine. This was similar to the studies done by Kopacz DJ et al,[10] Cox CR et al[8] in contrast to the study done by Bader AM et al,[3] Bay Nielsen et al[11] where they concluded that the motor blockade was similar between both the drugs.

Though there are limitations in this study since it was done with a smaller group but the results show similar outcome of studies that was done elsewhere. This study shows that epidural levobupivacaine produces a differential sensory - motor blockade and has a minimal incidence of side effects when compared to racemic bupivacaine Gristwood R Bardsley et al,[5] Bader AM et al,[6] Cox CR et al[8] (1998), Kopacz DJ et al[10] Bay Nielsen et al,[11] Kopacz DJ et al.[13]

Levobupivacaine is a safe and effective local anaesthetic for epidural anaesthesia requiring long lasting analgesia. The advantage of lower cardio toxicity and relatively lower motor blockade makes levobupivacaine a best choice for procedures where intense muscle relaxation is not necessary and also wherever greater amount of local anaesthetic is required - Gristwood R bardsley et al,[5] Bader AM et al,[6] Cox CR et al,[8] Kopacz DJ et al,[10] Burke D et al,[12] Kopacz DJ et al,[13] Lyons G et al,[14] Salomaki TE et al.[15]

One patient in the L group was excluded as the sensory blockade was patchy and asymmetrical and the other patient who was excluded as dural tap was suspected. Seven patients (28%) in racemic group had an episode of hypotension among which 3 patients (12%) needed vasopressor (ephedrine 6 mg once) to elevate their mean arterial pressure. One patient in L group had shivering and was treated with 25 mg of pethidine to control shivering. There was no incidence of any other complications like retention of urine, nausea, vomiting or local anaesthetic toxicity.

Conclusion

The efficacy of epidural levobupivacaine is comparable to that of racemic bupivacaine except for motor blockade.

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