COMPARING THE EFFICACY OF ISOBARIC LEVOBUPIVACAINE (0.5%) VERSUS HYPERBARIC BUPIVACAINE (0.5%) WITH FENTANYL 25µg FOR SUBARACHNOID BLOCK IN PATIENTS UNDERGOING UROLOGICAL PROCEDURES"

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ABSTRACT

BACKGROUND: Intrathecal opioids added to low dose local anesthetics in spinal anaesthesia intensifies sensory block without affecting sympathetic blockade. Aim was to evaluate the safety and efficacy of intrathecal 0.5% levobupivacaine plus fentanyl 25µg versus 0.5% bupivacaine plus fentanyl 25µg in patients undergoing urological procedures under subarachnoid block.

MATERIALS AND METHODS: In a prospective randomized double blind study, 60 patients of American Society of Anesthesiologists grades I and II of either sex, 18–75 years of age were included after approval from the Ethics Committee. Informed consent was taken and patients were randomly divided into two groups of 30 each, to receive either 3 ml of 0.5% isobaric levobupivacaine (group A) with 25µg fentanyl or 3 ml of 0.5% hyperbaric bupivacaine 25 µg fentanyl (group B) intrathecally. Patients were monitored for haemodynamics, sensory and motor block characteristics, postoperative analgesia, and side effects and complications for 24 hrs and side effects.

CONCLUSION: According to the findings of our study, subarachnoid block with 0.5% hyperbaric bupivacaine with 25µg fentanyl has earlier onset and longer duration of motor block when compared with 0.5% isobaric levobupivacaine with 25µg fentanyl. There is no difference in sensory block characteristics between the two groups**.** For day care and short duration procedure

and elderly patients, levobupivacaine may be preferred because of its shorter duration of motor block.

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INTRODUCTION

Spinal anaesthesia is the most safe and time-tested technique for administering anesthesia for urological surgeries due to its rapid onset and effective sensory and motor blockade [(1).] It is best preferred in urological surgeries because it is convenient for early detection of symptoms caused by over hydration, transurethral resection syndrome and bladder perforation [(2)]. There are different types of local anesthetics regarding pharmacokinetics and dynamics that anesthetist must be aware of before performing spinal anesthesia [(3)].It is the most common method for providing anesthesia and analgesia for lower abdominal and lower limb surgical procedures, as it gives intense sensory and motor blockade. The choice of local anaesthetics depends on its onset and duration of action and sensory – motor differential blockade. [(4)]

Bupivacaine, is widely used because of its long duration of action and good safety profile but it also resulted in cases with fatal cardiotoxicity especially in obstetrics. Bupivacaine is available as a racemic mixture of its enantiomers, dextrobupivacaine and levobupivacaine [(5)]

A study conducted by Gulen Guler et al stated that the evolution of the motor block was faster and lasted longer in Bupivacaine with Fentanyl group whereas hypotension, bradycardia and nausea were less in Levobupivacaine with Fentanyl group [(6)].

Levobupivacaine, the pure S (-) enantiomer of the racemic Bupivacaine was synthesized aiming at finding local anesthetics with better safety profile and with block strength as bupivacaine but without its hazards of cardiac and central nervous system toxicity [(7)]

A study conducted by F. Erdil et al concluded that levobupivacine along with fentanyl is a better and safe anesthetic drug for elderly people in urological procedures proving better

hemodynamics. Because of its significantly low side effects, levobupivacaine seems to be an attractive alternative to other drugs [8].

The addition of intrathecal fentanyl to spinal anesthesia is associated with an early time of onset of the anesthetic effect and a low incidence of side effects, also it prolongs the duration of action and spread of sensory block as well.

In this study we have compared and evaluated the time of onset and duration of sensory blockade, time of onset and duration of motor blockade and hemodynamic changes, side effects if any between isobaric levobupivacaine 0.5% with fentanyl 25µg and hyperbaric bupivacaine 0.5% with fentanyl 25µg for subarachnoid block in patients undergoing urological procedures.

Materials and Methods:

The study was a prospective randomized double blinded study conducted in the Department of Anaesthesiology and Critical Care , Chettinad Hospital & Research Institute, Kelambakkam, Chennai, after obtaining Institutional Human Ethics Committee approval (Proposal No..63/IHEC/9-1 on 17/10/2016). The study was conducted during the period 2016 to 2018. The study includes 2 groups of 30 patients each: Both groups received subarachnoid block with the respective study drug.

Group A (n=30) – 3.0 ml of Isobaric Inj Levobupivacaine 0.5% + Inj Fentanyl 0.5ml(25µg)

Group B (n=30) – 3.0 ml of Hyperbaric Inj Bupivacaine 0.5% + Inj Fentanyl 0.5ml (25µg)

Patients with age group between 18 to 75 years, American Society of Anesthesiologist (ASA) Grade I and II and all Elective/ Emergency urological procedures were included.

Patients who were not willing for regional anesthesia, patients not willing to be in the study group, pregnant patients, known allergy to the study drugs, patients with peripheral neuropathy were excluded.

Sampling

Maximum duration of sensory block was considered as the primary outcome in the study. The sample size was calculated considering the mean duration of sensory block in two groups as 168.30 and 172.20 minutes (As per study by Feroj A et al) with a common standard deviation of 5, an alpha error of 0.05 and 80% power of study. As per the above mentioned parameters, the required sample size was 27 participants per study group. To account for non-participation rate of about 10%, a total of 30 subjects was included in the study in each treatment arms.

The following formula was used for sample size calculation

$n = (Z_{\alpha/2}+Z_{\beta})^2 * 2*\sigma^2 / d^2$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84), σ^2 is the population variance (5 in this study), and d is the difference (2.86 in this study) you would like to detect.

METHODS

The selected patients underwent routine pre anaesthetic assessment. Informed written consent was obtained and patients were randomized into Group A and Group B by computer-generated randomization code. Allocation concealment was done using opaque sealed envelopes. Both groups received subarachnoid block with their respective drugs.

Group A(n=30): 3.0ml of Isobaric Inj Levobupivacaine 0.5 % + Inj Fentanyl 0.5ml (25µg)
Group B(n=30): 3.0 ml of Hyperbaric Inj Bupivacaine 0.5% + Inj Fentanyl 0.5ml (25µg)

All patients were kept nil oral 6 hours prior to surgery. On arrival to the operating room an iv access was established with 18 gauge IV cannula. Monitored variables include continuous Electrocardiogram (ECG), Heart rate (HR), Non invasive blood pressure(NIBP) and SpO_2. Baseline values was noted before the performance of the subarachnoid block.

Under aseptic precautions in sitting position L3-L4 inter-space was infiltrated with 2ml of 2% Inj.Lignocaine. The subarachnoid space was entered at L3-L4 inter-space via the midline approach using 26 gauge Quincke spinal needle. The correct needle placement was identified by free flow of cerebrospinal fluid. The study drug was injected by the anesthetist blinded to the study. Patient was placed in supine position to carry over the initial assessment. Patient's Heart rate, Blood pressure, Oxygen saturation, were monitored at 1 min, 3min, 5 min and then every 5 minutes till 60 minutes then every 10 minutes till end of the procedure . Throughout the procedure, the patient received 5 liters of oxygen per minute through facemask. The anaesthetist blinded to study drug assessed the sensory and motor block throughout.

1. **Onset of sensory block** was assessed by the changes in sensation to cold pack every minute till no sensation (Grade 2) is achieved, which is graded according to Gromley and Hill 1996

Normal sensation – grade 0

Blunted sensation – grade 1

No sensation – grade 2.

Grade 2 was taken as onset of sensory block.

2. **Onset of motor block** was assessed every minute till complete motor block (Grade 1) is achieved, which is graded according to modified Bromage scale.(Table:3)

Table:3 Modified Bromage Scale

Score	Criteria
1	Complete block (unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (able to move knees)
4	Detectable weakness of hip flexion while supine(full flexion of knees)

5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

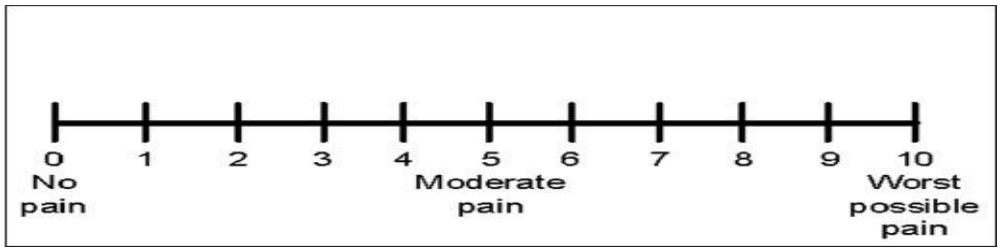
3. **Duration of sensory block** was taken as the time from the onset of sensory block to the time when the VAS>1 post-operative pain.

4**. Duration of motor block** (recovery of motor blockade to Grade 4) was taken from complete motor block to the time when the patient recovers the ability to flex the knees.

If the subarachnoid block was found to be inadequate the procedure was converted to general anesthesia and the patient was excluded from the study. Regression time to T10 sensory level sensory level was recorded.

Postoperative monitoring of pain was assessed with the help of visual analogue score (VAS) using a 10 cm line, where zero denotes no pain and 10 denotes worst possible pain. Pain score was assessed after 150 minutes following SAB and monitored every 30 minutes thereafter; till the patient complains of pain. If VAS > 1 Injection Tramadol 50 mg slow iv was given. Patient was monitored for recovery of motor function every 3 minute till Bromage score of 4

Visual analogue score



Side effects like hypotension (defined as fall in systolic blood pressure to less than 100mmHg or decrease in mean blood pressure of more than 20% from base line was treated with 6mg of Inj.Ephedrine bolus, bradycardia (Heart

rate < 50/min was treated with 0.6 mg of Inj.Atropine) ; nausea, vomiting, shivering, respiratory depression and were treated appropriately.

Nausea, vomiting was treated with Inj. Ondansetron 4mg after excluding hypotension and hypoxia. Shivering was treated only conservatively with warm fluids. Respiratory depression was watched out.

STATISTICAL METHODS

Onset motor block, onset sensory block (minutes) were considered as primary outcome variables.

SBP, DBP, heart rate, mean arterial pressure were considered as secondary outcome variables.

Study group (levobupivacaine Vs bupivacaine) was considered as Primary explanatory variable.

All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution.

For normally distributed Quantitative parameters the mean values were compared between study groups using Independent sample t-test (2 groups). Data was also represented using appropriate diagrams like comparative error bar chart.

Categorical outcomes were compared between study groups using Chi square test. Data was also represented using appropriate diagrams like Clustered bar chart and stacked bar chart.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.(1)

1. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Result:

All demographic date such as age, gender and study group disease were compared and there is no statistically significant difference between the two groups.

Table 1: Comparison of mean onset of motor block (minutes) between study groups (N=60)

Study group	Onset motor block (Minutes) Mean± SD	Mean difference	95% CI		P value
			Lower	Upper	
Levobupivacaine	4.97 ± 1.47	2.20	1.54	2.86	***<0.001***
Bupivacaine	2.77 ± 1.04				

The mean onset motor block of levobupivacaine group was 4.97 ± 1.47 and bupivacaine group was 2.77 ± 1.04, and the mean difference (2.20) in the onset motor block MBS between two groups was statistically significant (P value <0.001). (Table 1)

Table 2: Comparison of mean onset of (T10) sensory block (minutes) between study groups (N=60)

Study group	Onset sensory block (minutes) Mean± SD	Mean difference	95% CI		P value
			Lower	Upper	
Levobupivacaine	1.7 ± 1.37	0.30	- 0.43	1.03	**0.411**
Bupivacaine	2 ± 1.44				

The mean onset sensory block of levobupivacaine group was 1.7 ± 1.37 and bupivacaine group was 2 ± 1.44, and the mean difference (0.30) in the onset sensory block between two groups was statistically not significant (P value 0.411). (Table 2)

Table 3: Comparison of mean time taken to achieve T6 (mins) between study groups (N=51)

Study groups	Time taken to achieve T6 (mins) Mean ± SD	Mean difference	95% CI		P value
			Lower	Upper	
Levobupivacaine	5.04 ± 2.13	0.20	-0.99	1.39	**0.739**
Bupivacaine	4.84 ± 2.1				

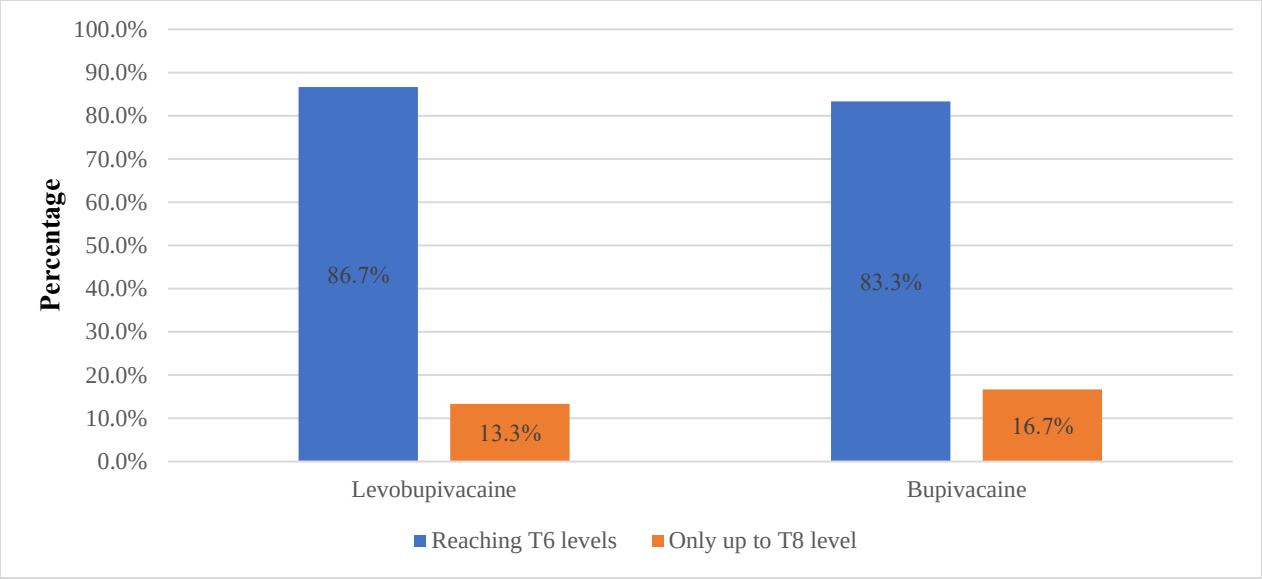
The mean time taken to achieve T6 (mins) of levobupivacaine group was 5.04 ± 2.13 and bupivacaine group was 4.84 ± 2.1, and the mean difference (0.20) in the time taken to achieve T6 (mins) between two groups was statistically not significant (P value 0.739). (Table 8 & Figure 7)

Table 4: Comparison of group with level of sensory block (N=60)

Level of sensory block	Group		Chi square	P-value
	Levobupivacaine (N=30)	Bupivacaine (N=30)		
Reaching T6 levels	26 (86.66%)	25 (83.33%)	0.131	**0.718**
Only up to T8 levels	4 (13.33%)	5 (16.66%)		

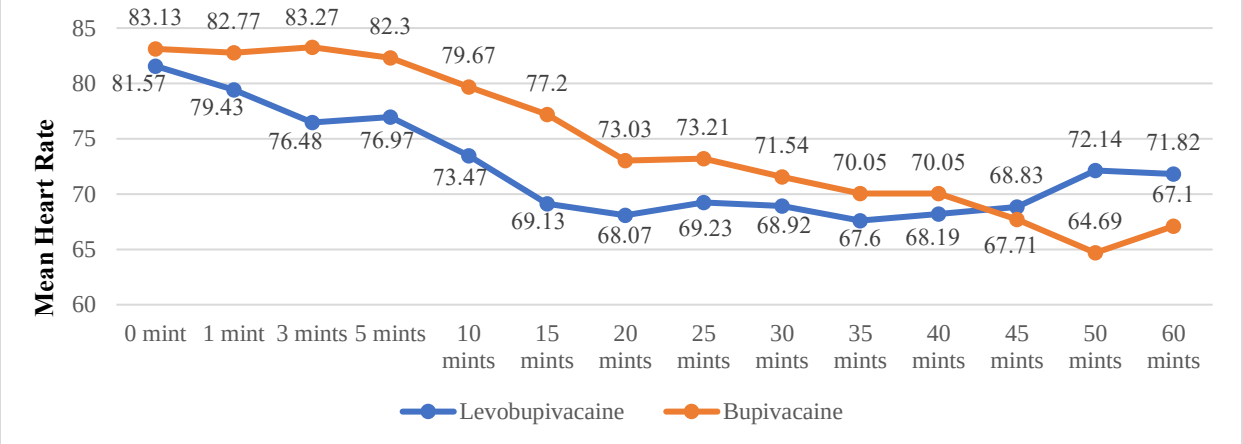
In levobupivacaine group, 26 (86.66%) participants were reaching T6 levels and 4 (13.33%) participants were only up to T8 levels. In bupivacaine group, 25 (83.33%) participants were reaching T6 levels and 5 (16.66%) participants were only up to T8 levels. The difference in the proportion of level of sensory block between study group was statistically not significant (P value 0.718). (Table 4)

Figure 2: Clustered bar chart of comparison of group with level of sensory block (N=60)



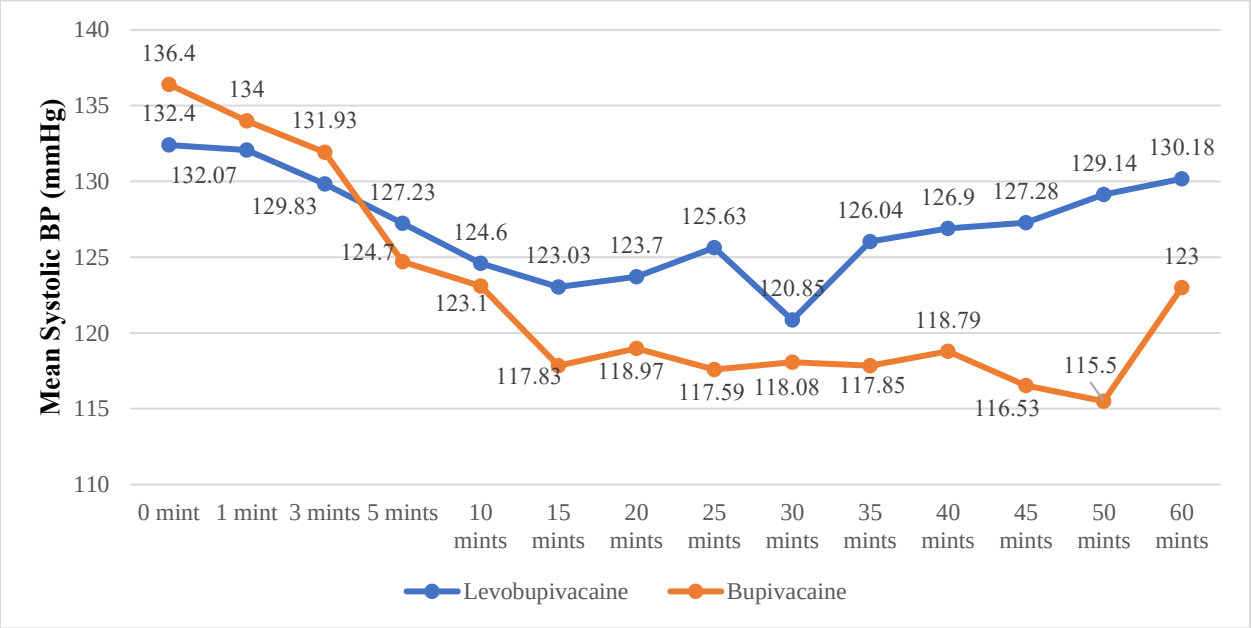
There was no statistically significant difference between two groups in heart rate various follow up time periods (P> 0.05). The mean 15 minutes heart rate of levobupivacaine group was 69.13 ± 14.19 and bupivacaine group was 77.2 ± 16.11, and mean difference between two groups in the heart rate at 15 minutes was statistically significant (P value 0.044). (Figure 1)

Figure 1: Trend line diagram of comparison of Mean Heart Rate between study groups



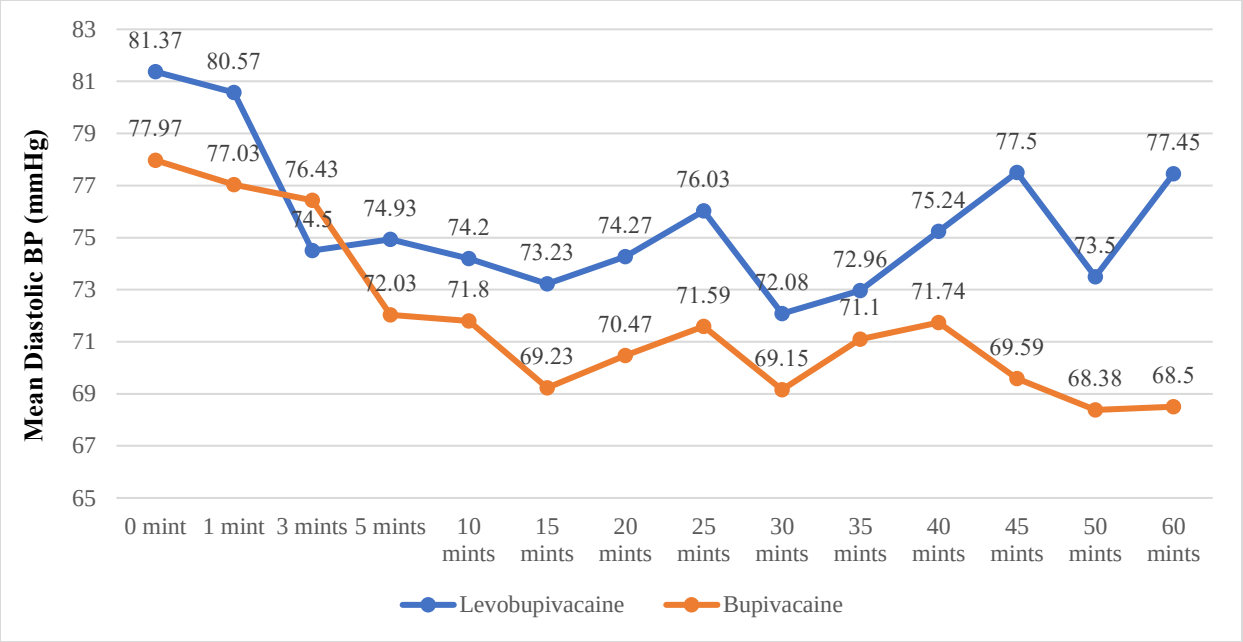
There was no statistically significant difference between two groups in systolic blood pressure various follow up time periods (P> 0.05). (Figure 2)

Figure 2: Trend line diagram of comparison of Mean Systolic BP (mmHg) between study groups



There was no statistically significant difference between two groups in diastolic blood pressure various follow up time periods (P> 0.05). (Figure 2)

Figure 3: Trend line diagram of comparison of Mean Diastolic Blood Pressure (mmHg) between study groups



There was no statistically significant difference between two groups in mean arterial pressure various follow up time periods (P> 0.05). The mean arterial pressure at 45 minutes of levobupivacaine group was 88.89 ± 12.78 and bupivacaine group was 80.33 ± 11.89 and mean difference between two groups in the mean arterial pressure at 45 minutes was statistically significant (P value 0.045). (Figure 2)

Figure 3: Trend line diagram of comparison of mean arterial pressure between study groups

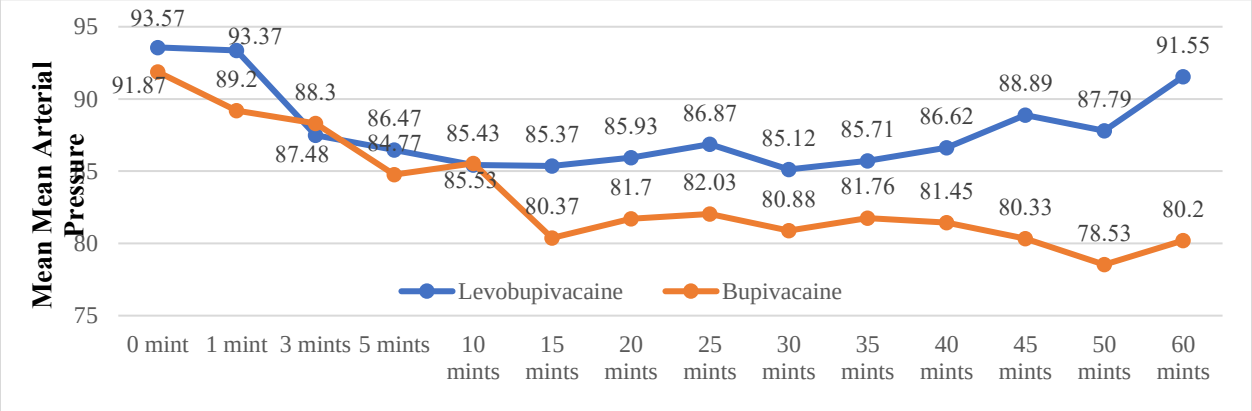


Table 5: Comparison of mean duration of motor block (minutes) between study groups (N=60)

Study group	Duration of motor (minutes) Mean± SD	Mean difference	95% CI		P value
			Lower	Upper	

Levobupivacaine	195 ± 25.83	48.00	31.69	64.31	***<0.001***
Bupivacaine	243 ± 36.4				

The mean duration of motor block (mins) of levobupivacaine group was 195 ± 25.83 and bupivacaine group was 243 ± 36.4, and the mean difference (48) in the duration of motor block (mins) between two groups was statistically significant (P value <0.001). (Table 5)

Table 6: Comparison of mean of duration of sensory block (minutes) between study groups (N=60)

Study group	Duration of sensory block (minutes) Mean± SD	Mean difference	95% CI		P value
			Lower	Upper	
Levobupivacaine	230 ± 47.49	23.00	-2.50	48.50	**0.076**
Bupivacaine	207 ± 51.14				

The mean duration of sensory block (mins) of levobupivacaine group was 5.04 ± 2.13 and bupivacaine group was 4.84 ± 2.1, and the mean difference (0.20) in the duration of sensory block (mins) between two groups was statistically not significant (P value 0.076). (Table 6)

Table 7: Comparison of mean regression time to T 10 (minutes) between study groups (N=60)

Study group	Regression time to T 10 (Minutes) Mean± SD	Mean difference	95% CI		P value
			Lower	Upper	
Levobupivacaine	207 ± 40.44	26.00	5.43	46.57	***0.014***
Bupivacaine	233 ± 39.14				

The mean regression time to T10 (mins) of levobupivacaine group was 207 ± 40.44 and bupivacaine group was 233 ± 39.14, and the mean difference (26) in the regression time to T10 (mins) between two groups was statistically significant (P value 0.014). (Table 7).

DISCUSSION

Our study has shown that levobupivacaine proven to have lesser cardio toxicity profile, has not shown any significant advantage over bupivacaine in terms of onset and duration of sensory and motor block. Rather bupivacaine has shown earlier onset of motor block and longer duration of motor block. In our study we recruited only patients undergoing urological procedures which included of ureteroscopic lithotripsy (URSL) procedures, wherein depending upon the location and number of stones, the procedure can last even 2-3 hours. So, we chose a volume of 3.0 ml of the study drug along with fentanyl 25µg in both groups. In such type of surgeries we prefer a longer duration of motor block.

In our study , we have compared hyperbaric bupivacaine, since it is been routinely used and commonly available with recently introduced isobaric levobupivacaine to see if isobaric levobupivacaine offered any significant advantage in block characteristics.

Many studies have shown similar results as our study showing that hyperbaric bupivacaine has earlier onset and longer duration of motor block than isobaric 0.5% levobupivacaine. In our study the mean difference in duration of motor blockade is 48.0 mins with confidence interval of to 31.69 to 64.31mins. The effect size was larger as we used a higher dose of the study drug.

Gautier et al[9], also has shown that bupivacaine provides significantly longer duration of motor block than levobupivacaine although they used isobaric 0.5% concentrations of both study drugs with sufentanyl as additive in both groups. According to their study the duration of analgesia was also longer in the bupivacaine group.

Erdil et al[10], in their study found that the time to onset of motor block was 19.1±5.4 mins in the group receving 1.5 ml of plain 0.5% levobupivacaine group with 15µg fentanyl and 9.5± 4.2 mins in the group receiving 1.5 ml of 0.5% plain bupivacaine with 15µg fentanyl. Again in this study bupivacaine has shown an earlier onset of motor block though it was isobaric and the earlier onset was longer than our study ,because the dose in this study was lesser than in our study. Yet both groups have shown comparable duration of motor block. It could be because both drugs were isobaric.

Guler et al[11], in his study found that the regression time of the sensory block to T12 and the duration of sensory block was significantly longer for the bupivacaine group. They have compared 2ml of 0.5% levobupivacaine plus 15µg fentanyl with 2ml of 0.5% hyperbaric bupivacaine plus fentanyl 15µg in caesarean section. Duration of motor block in the bupivacaine group was significantly longer (132.66±7.5 versus 99±9.13mins). It was obviously lesser than our study due to the lesser volume used in their study. Hemodynamic was better in the levobupivacaine group.

Duggal et al [12], has shown similar results as in our study with significant difference in onset of motor block and duration of motor block in bupivacaine group. They also found that the duration of sensory block was significantly more in bupivacaine group. They have compared 2ml of 0.5% levobupivacaine and 2ml of 0.5% hyperbaric bupivacaine intrathecally without any additive for caesarean section.

Sivakumar et al [13], in their study has shown a significance difference in the duration of sensory block (regression to T12 dermatomal level)with longer duration in the isobaric levobupivacaine group of 2.5ml group when compared to the bupivacaine group of 2.5ml but the motor block was longer in bupivacaine group when compared to the levobupivacine group. Our study did not show any significant difference in the duration of sensory block as we defined it from the onset of sensory block to patient pain score assessment of visual analogue score (VAS) > 1. Whereas their study assessed it till regression to T12 level. Procedures like Uteroscopic Lithotripsy (URSL) showed earlier onset of pain score(VAS) greater than 1.
In the study by Akan et al[14], the onset of sensory block was 6.9±1.7 min in the group receiving intrathecal 7.5 mg of 0.5% levobupivacaine with 25µg of fentanyl. Whereas our study showed onset of sensory block in levobupivacaine group of 1.7±1.37 min. The difference in the readings could be explained by the fact that they have used lesser dose of drugs that is 7.5mg of 0.5% levobupivacaine with 25µg fentanyl.

CONCLUSION:

According to the findings of our study, subarachnoid block with 0.5% hyperbaric bupivacaine with 25µg fentanyl has earlier onset and longer duration of motor block when compared with 0.5% isobaric levobupivacaine with 25µg fentanyl. There is no difference in sensory block characteristics between the two groups**.** For day care and short duration procedure and elderly patients, levobupivacaine may be preferred because of its shorter duration of motor block.

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