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A comparative study of low-dose intrathecal bupivacaine 0.5% (heavy), levobupivacaine 0.5% (plain), and levobupivacaine 0.5% (heavy) with fentanyl as an adjuvant in transurethral resection of prostate surgery: A prospective randomized study

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ABSTRACT

Background: Spinal anesthesia is the technique of choice for transurethral resection of the prostate (TURP) surgeries. Levobupivacaine, an S-enantiomer of bupivacaine, is less cardiotoxic than bupivacaine; therefore, a low dose of local anesthetic with fentanyl as an adjuvant has been used to decrease toxicity and increase efficacy. **Aims and Objectives:** The aim of this study was to compare and evaluate the efficacy of hyperbaric bupivacaine 0.5%, isobaric levobupivacaine 0.5%, and hyperbaric levobupivacaine 0.5% with fentanyl as an adjuvant. **Materials and Methods:** One hundred and five patients scheduled for elective TURP surgeries were randomly divided into three groups. Group BH (n = 35) received 1.5 mL of 0.5% hyperbaric bupivacaine with 25 μg of fentanyl, Group LH (n = 35) received 1.5 mL of 0.5% hyperbaric levobupivacaine with 25 μg of fentanyl, and Group LP (n = 35) received 1.5 mL of 0.5% isobaric levobupivacaine with 25 μg of fentanyl intrathecally. **Results:** The onset of sensory and motor block was earlier and the duration of analgesia and motor block were longer in the BH group ($P < 0.001$) as compared to LH and LP groups. The demographic data, duration of surgery, heart rate, SpO_2, pruritus, and shivering were comparable between the groups ($P > 0.05$). The visual analog scale score was higher in the LP group. Hypotension, nausea, and vomiting were seen in the BH group. **Conclusion:** Hyperbaric is better than isobaric group due to quicker onset and longer duration. Levobupivacaine is better than bupivacaine in terms of the early mobilization and a lesser incidence of side effects, making hyperbaric levobupivacaine a better alternative to isobaric levobupivacaine and hyperbaric bupivacaine.

Key words: Hyperbaric; Isobaric; Levobupivacaine; Bupivacaine; Intrathecal fentanyl; Spinal anesthesia; Transurethral resection of the prostate

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INTRODUCTION

Spinal anesthesia is the technique of choice for transurethral resection of the prostate (TURP). TURP patients are particularly vulnerable to volume overload, as the majority of them are elderly and suffer from cardiopulmonary disorders. Spinal anesthesia helps in peripheral pooling of blood, reducing the chance of circulatory overload and early detection of TURP syndrome and bladder perforation. It also provides post-operative analgesia, reduces blood loss during surgery, and avoids the necessity of tracheal intubation, which might worsen the airway,

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leading to coughing and straining, and may exacerbate post-operative hemorrhage. In addition, it reduces deep vein thrombosis, which is beneficial for TURP patients.[1,2] Thus, spinal anesthesia is usually recommended so that early signs of neurological deterioration can be detected.[3]

For spinal anesthesia, hyperbaric preparations of local anesthetics are preferred over isobaric solutions because they result in a more dependable and consistent sensory and motor block that has a longer duration, a quicker onset,[4] and fewer side effects which include high block, hypotension, nausea and vomiting, and pruritus.[5] They quicken the regression of sensory blocks and the recovery of motor blocks.[6,7] Isobaric solutions have a slower, less intense, shorter onset, and duration and are not associated with any significant hemodynamic alterations.

Low-dose local anesthesia limits spinal block level and enhances rapid recovery from anesthesia. The segmental sympathetic blockade is less, which, in turn, provides better hemodynamics. High doses can cause cardiovascular instability, and decreased interspinous spaces will lead to a high level of block, causing hemodynamic instability and prolonging motor block in elderly patients, which can increase the duration of immobilization after surgery and increase the risk of thromboembolism.[8,9]

Several adjuvants have been used, such as fentanyl, sufentanil, tramadol, clonidine, and dexmedetomidine, which can prolong the duration of analgesia and decrease the local anesthetic dose requirement, thereby decreasing the risk of toxicity. Fentanyl, a lipophilic opioid that binds tightly to plasma proteins and improves afferent sensory blockade, has been used as an adjuvant in this study to facilitate a reduction in the dosage of local anesthetic.[8]

Intrathecal administration of opioids and local anesthetics together has potent synergistic analgesic effects that improve sensory blockade without changing the degree of sympathetic blockade, ensuring improved hemodynamic outcomes.[10]

In this prospective and randomized double-blind study, we compared low-dose 0.5% bupivacaine heavy, 0.5% levobupivacaine plain, and 0.5% levobupivacaine heavy with fentanyl as an adjuvant in elective TURP surgeries under spinal anesthesia.

Aims and objectives

To compare and evaluate the efficacy of hyperbaric bupivacaine 0.5%, isobaric levobupivacaine 0.5%, and hyperbaric levobupivacaine 0.5% with fentanyl as an adjuvant.

Primary objective

To compare onset and duration of sensory and motor block between the groups.

Secondary objective

To compare intraoperative haemodynamic parameters and side effects between the groups.

MATERIALS AND METHODS

After the Institutional Ethics Committee approval, the study was conducted at G. R. Medical College and JAH group of hospitals during 2022–2024. One hundred and five patients of ASA Grades I and II, aged 50–75 years, who were scheduled for elective TURP surgery under spinal anesthesia were included in our study.

The sample size was calculated from the study done by Vanna et al.[1]

$$n = 2\ S2\ (Z\alpha + Z1\text{-}ß)2/(\mu1\text{-}\mu2)$$

where, S=3.96
$Z\alpha$=1.96, Z1-ß= 0.84
$\mu1$-$\mu2$-= 2.7

We obtained n=34, that is, approximate to 35. Hence, 35 patients were assigned under each of the three groups; therefore, the total sample size required for the study was 105.

Inclusion criteria

Patients giving consent, aged between 50 and 75 years, and belonging to ASA Grade I and II were included in the study.

Exclusion criteria

Uncooperative patient, patients with respiratory, cardiovascular, hepatic, and renal diseases, obesity, neurological diseases (multiple sclerosis, symptomatic lumbar herniated disc, spinal stenosis, etc.), coagulopathy, or local infection were excluded from the study.

Patients were randomized into three groups by sealed envelope method based on the local anesthetic drug used intrathecally in a double-blinded manner (the drug was prepared by an anesthesiologist other than the investigator and the drug was injected and the parameters were studied by the investigator).

i. Group BH (n=35): 0.5% Bupivacaine heavy (1.5 mL) + 25 µg Fentanyl (0.5 mL)
ii. Group LH (n=35): 0.5% Levobupivacaine heavy (1.5 mL) + 25 µg Fentanyl (0.5 mL)
iii. Group LP (n=35): 0.5% Levobupivacaine plain (1.5 mL) + 25 µg Fentanyl (0.5 mL)

Pre-anesthetic assessment was done to screen or evaluate major systemic illnesses, and informed written consent was taken from all patients after explaining the purpose and protocol of the study.

All the patients were examined a day before surgery for complete general, physical, and systemic examination. All the required routine and special investigations including complete blood count, random blood sugar, blood urea, serum creatinine, liver function test, coagulation profile, serum electrolyte, ECG, and chest X-ray were done as per hospital protocol.

All patients were kept nil orally for at least 6 h before the procedure.

On arrival of the patient in the operation theater, an 18 G cannula was inserted intravenously into the patient's forearm. All routine parameters including pulse oximeter, blood pressure (BP) cuff, and ECG were connected and observations were recorded using CARESCAPE B650 monitor. Pre-loading was done with approximately 10 mL/kg of normal saline solution.

Under all aseptic precautions, lumbar puncture was done in a sitting position at the L3–L4 intervertebral space through midline approach using a 25G Quincke spinal needle. Subarachnoid block was performed, the study drug was injected and the patient was positioned in the supine position for the remainder of the study period. The surgeon was allowed to start the procedure after a sensory block of at least T10 level was reached. The following parameters were studied for statistical analysis.

1. Time of onset of sensory block (up to T10) was assessed by loss of pinprick sensation
2. Time for onset of motor block (Bromage 3) was assessed by a modified Bromage scale
   0=no motor block
   1=able to flex the knee (hip blocked)
   2=able to dorsiflex the foot (knee and hip blocked)
   3=Complete motor block (hip, knee, and ankle blocked)
3. Peak level of sensory block and time to reach the peak level of sensory block
4. Duration of sensory block defined as from time of induction to S1 regression from peak dermatome level
5. Duration of motor block (Bromage 0)
6. Duration of analgesia, defined as from induction of spinal anesthesia to onset of pain (i.e., visual analog scale [VAS] score ≥ 3 or request of first analgesic supplement)
7. Post-operative VAS score was assessed by VAS (where 0 means no pain and 10 means the worst pain imaginable) at 0 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, and 10 h post-surgery where a number of patients with VAS score ≥3 was recorded at different interval of time. The study was stopped when the VAS score reached ≥3 and was managed with injection tramadol 2 mg/kg i.v. in 100 mL normal saline to relieve post-operative pain
8. Assessment of hemodynamic parameters intraoperatively including heart rate (HR), systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and SpO_2 at 0, 3, 5, 10, 15, 30, 60, and 90 min after induction. Any fall in BP below 20% of baseline value was treated with a bolus dose of injection mephentermine 6 mg i.v. HR <50 beats/min was treated with injection atropine sulfate 0.3–0.6 mg i.v.
9. Observation and recording of any side effect or complication related to the study drug.

Data were composed in suitable spreadsheet, that is, EXCEL and SPSS. After the compilation of data, it was analyzed statistically by SPSS software version 20.0. Statistical tests used to compare three groups were ANOVA t-test and *post hoc* Tukey test. The significance level was 95% confidence level ($P<0.05$).

RESULTS

The demographic characteristics such as age and weight were comparable between all three groups, which was statistically insignificant ($P>0.05$), as shown in Table 1.

The onset of sensory and motor block and the time to reach peak level of sensory block was earlier in the BH group whereas the duration of sensory and motor block, and duration of analgesia was prolonged in the BH group which was statistically significant ($p < 0.001$), as shown in Table 2. The highest level of sensory block achieved was T8 in a few patients and T10 in the maximum number of patients.

The mean HR was comparable between the groups which was statistically insignificant ($P>0.05$).

Table 1: Demographic profile (Mean±SD)

Demographic parameter	BH (n=35)	LH (n=35)	LP (n=35)	P-value
Age (years)	66.11±6.69	65.40±7.53	64.43±6.64	0.599
Weight (in kg)	60.89±6.75	59.74±7.00	57.14±7.83	0.089

P>0.05 insignificant, *P<0.05 significant, **P<0.001 highly significant

Table 2: Parameters of spinal anesthesia

Parameters	BH (n=35)	LH (n=35)	LP (n=35)	P-value
Onset of sensory block at T10 (min)	04:51±00:22	06:25±00:40	07:45±00:46	**<0.001
Time to reach peak level of sensory block (min)	04:53±00:23	06:29±00:41	07:55±00:57	**<0.001
Duration of sensory block (min)	150.4±13.97	131.77±16.48	126±13.71	**<0.001
Time of onset of motor block (min)	05:18±00:20	06:37±00:42	08:45±00:46	**<0.001
Duration of motor block (min)	117±14.17	104.34±14.86	94.45±12.99	**<0.001
Duration of analgesia (min)	180.74±13.68	162.05±17.28	156.25±13.66	**<0.001

P>0.05 insignificant, *P<0.05 significant, **P<0.001 highly significant

The mean SBP, DBP, and MAP showed a significant difference where a dip was seen in SBP after 5 min with the lowest SBP at 15 min after spinal anesthesia and the DBP and MAP was lower after 3 min up to 60 min in BH group patients (P<0.001), as shown in Figure 1.

VAS score ≥3 was found in five patients in the LP group (14.3%) and three patients in LH group (8.6%) at 1st h. It was also observed in 30 patients in LP group (85.7%), 31 patients in LH group (88.6%), and 26 patients in BH group (74.3%) at 2nd h post-surgery. None of the patients in LP group showed VAS score ≥3 after 2nd h as they had received rescue analgesia. VAS score ≥3 was seen in one patient in LH group (2.9%) and nine patients in BH group (25.7%) at 3rd h post-surgery. Therefore, rescue analgesia was needed earlier in LP group as compared to BH and LH groups, as seen in Figure 2.

The incidence of nausea, vomiting, and hypotension was seen in BH group and none of the patients in LH and LP groups. Shivering and pruritus were comparable in all three groups, as shown in Table 3.

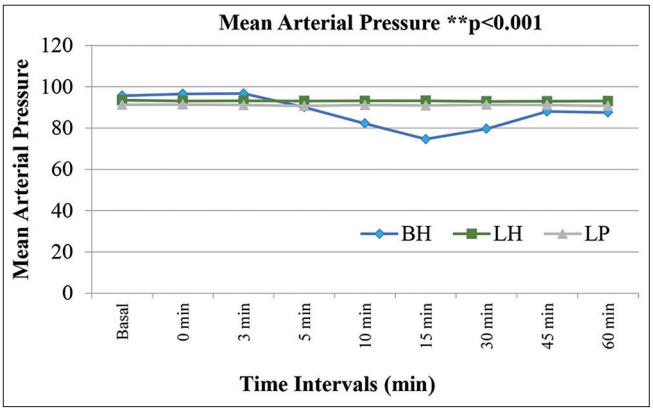

Figure 1: Intraoperative mean arterial pressure

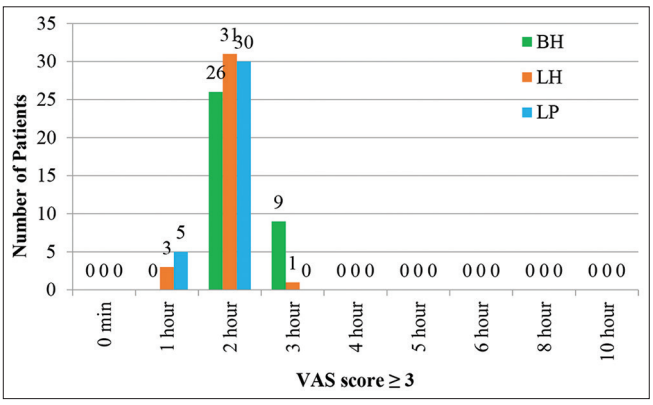

Figure 2: Post-operative visual analog scale score

DISCUSSION

Spinal anesthesia is preferable for TURP surgeries as it reduces volume overload in elderly patients who already have compromised cardiopulmonary function. It helps in the early detection of complications such as TURP syndrome and provides better post-operative analgesia. The most commonly used local anesthetic is bupivacaine, which is associated with cardiotoxicity. However, its S (-) enantiomer, levobupivacaine, has fewer effects on the cardiovascular and central nervous system due to its faster protein-binding rate. Compared to isobaric solutions, hyperbaric solutions offer a dependable sensory and motor block with a quicker onset, longer duration, and fewer side effects. Low-dose local anesthesia induces rapid recovery from anesthesia, and the addition of an adjuvant like fentanyl can prolong the duration of analgesia and decrease the local anesthetic dose requirement.

In the present study, the demographic variables were comparable between all three groups and were statistically insignificant (P>0.05), similar to the studies of Vanna et al.[11] (Table 1).

The time of onset of sensory block at T10 was earlier in the BH group compared to the LH and LP groups, which was highly significant (P<0.001). Similar results were found in a study done by Sen et al.,[12] where the onset was earlier in the LH group compared to the LP group. Similarly, Goyal et al.,[13] and Thakore et al.,[14] found an earlier onset in the BH group than in the LH group. Saha et al.,[15] found in their study that the onset was earlier in the BH group than in the LP group (Table 2).

The time to reach peak level of sensory block was shorter in the BH group compared to the LH and LP groups (P<0.001). Similar results were seen in the study done

Table 3: Side effects/Complications

Side effects/Complications	BH	LH	LP	P-value
	No. of patients (%)	No. of patients (%)	No. of patients (%)	
Nausea	2 (5.7)	0 (0.0)	0 (0.0)	0.130
Vomiting	5 (14.3)	0 (0.0)	0 (0.0)	**0.005
Hypotension	4 (11.4)	0 (0.0)	0 (0.0)	*0.016
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	-
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	-
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	-
Pruritus	1 (2.9)	1 (2.9)	1 (2.9)	1.000
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	-
Shivering	3 (8.6)	5 (14.3)	6 (17.1)	0.562

P>0.05 insignificant, *P<0.05 significant, **P<0.001 highly significant

by Sen et al.,[12] where the time to reach the peak level was shorter in the LH group than in the LP group, and shorter in the BH group than in the LH group, as seen in the study done by Thakore et al.[14] (Table 2).

The duration of sensory block was prolonged in the BH group compared to the LH and LP groups. Similar results were found in the study by Choudhary et al.,[16] where duration was longer in the BH group than in the LP group whereas contrasting results were found by Goyal et al.,[13] where it was shorter in the BH group. Akcaboy et al.,[17] and Oraon et al.,[18] found similar results in both the BH and LP groups. Sen et al.,[12] found contrasting results where duration was longer in LP group than LH groups. Luck et al.,[19] found that the duration was longer in the BH group than in the LH group whereas Thakore et al.,[14] found contrasting results and Subaşı et al.,[20] found no difference (Table 2).

The time of onset of motor block was quicker in the BH group and was highly significant (P<0.001). Similar results were found in the study by Hakan Erbay et al.,[21] Goyal et al.,[13] and Thakore et al.,[14] where the onset was earlier in the BH group than in the LH group. Sen et al.,[12] found an earlier onset with the LH group than in the LP group. Saha et al.,[15] also found similar results where the BH group had an earlier onset than the LP group (Table 2).

The duration of motor block was longer in the BH group than in the LH and LP groups. Similar results were found in the study by Hakan Erbay et al.,[21] Goyal et al.,[13] and Thakore et al.,[14] where the duration was prolonged in the BH group compared to the LH group (Table 2).

The duration of analgesia was prolonged in the BH group compared to the LH and LP groups. Similar results were found in the study by Choudhary et al.,[16] and Goyal et al.,[13] where duration was longer in the BH group than in the LP group. Contrasting results were seen in a study done by Saha et al.,[15] where it was shorter in the BH group compared to the LP group. Akcaboy et al.,[17] and Oraon et al.,[18] found similar results in both the BH and LP groups. Sen et al.,[12] found no difference between the LH and LP groups. Luck et al.,[19] and Subaşı et al.,[20] found similar results where the duration was longer in the BH group than in the LH group. Thakore et al.,[14] found contrasting results where the duration was longer in the LH group compared to the BH group (Table 2).

A fall in SBP, DBP, and MAP was seen in the BH group which was statistically significant (P<0.001). No significant changes were seen in SBP, DBP, and MAP in the LH and LP groups. Similar results were found in the study by Herrera et al.,[22] where a fall in SBP and DBP was seen at 30 min intraoperatively. Singh et al.,[23] and Goyal et al.,[13] found that hypotension was more evident in the BH group than in the levobupivacaine group (Figure 1).

In our study, VAS score ≥3 in patients of the LH and LP groups were more common in the 1st h and 2nd h post-surgery compared to the BH group, where VAS score ≥3 was seen in the 2nd h post-surgery, showing more effective pain control by the BH group. Similar results were seen in the study done by Subaşı et al.,[20] where the need for rescue analgesia was earlier in the LH group than in the BH group.

Contrasting results were found by Hakan Erbay et al.,[21] where rescue analgesia was needed earlier in the BH group than in the LH group (Figure 2).

The incidence of nausea, vomiting, and hypotension was seen in the BH group and not in patients of the LH and LP groups. The incidence of pruritus and shivering was comparable between all three groups. Fernandez-Galinski et al.,[10] and Girgin et al.,[24] found the incidence of pruritus in patients of the hyperbaric bupivacaine with fentanyl and levobupivacaine with fentanyl groups, respectively.

Limitations of the study

One limitation was the small sample size of our study. A multicentric large population study should be carried out to obtain more appropriate and certain results.

Another limitation was the difficulty for the investigator to measure and assess post-operative pain objectively since pain is a subjective experience.

CONCLUSION

We concluded from this study that the sensory and motor block occurred more quickly and lasted longer in the bupivacaine heavy group compared to the levobupivacaine heavy and levobupivacaine plain groups. Intraoperative hypotension and side effects such as nausea and vomiting were seen in the bupivacaine heavy group. Levobupivacaine heavy is a better alternative to bupivacaine heavy in terms of hemodynamic stability and early mobilization. Levobupivacaine heavy provides better post-operative analgesia compared to the levobupivacaine plain group.

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