Original Research

COMPARATIVE EFFECT OF INTRATHECAL HYPERBARIC LEVOBUPIVACAINE VERSUS BUPIVACAINE WITH MIDAZOLAM AS ADJUVANT IN LOWER LIMB SURGERY

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ABSTRACT

Background and Objectives: The search for a cardio-stable local anaesthetic with a superior safety profile has led to the increased use of levobupivacaine. This study aimed to compare the clinical efficacy and safety of hyperbaric levobupivacaine versus hyperbaric bupivacaine, both using midazolam as an intrathecal adjuvant, in patients undergoing lower limb surgeries.

Materials and Methods: In this prospective, randomized, double-blind study, 60 ASA I and II patients aged 15–75 years were divided into two equal groups (n=30). **Group B** received 2.8 ml of 0.5% hyperbaric bupivacaine with 1 mg preservative-free midazolam, while **Group L** received 2.8 ml of 0.5% hyperbaric levobupivacaine with 1 mg midazolam. The primary objective was to compare the onset of sensory and motor blockade. Secondary objectives included the assessment of hemodynamic changes, duration of analgesia, sedation levels (OAA/S scale), and the incidence of adverse effects.

Results: The mean time to sensory block onset at the T10 level was significantly faster in **Group B** (3.2 ± 0.92min) than in **Group L** (4.06 ± 1.14 min; p=0.002). However, motor block onset times (4.69 vs. 5.00 min; p=0.36) and total duration of motor blockade (3.21 vs. 3.2 hours; p=0.95) were comparable. **Group L** demonstrated significantly greater hemodynamic stability, maintaining higher Mean Arterial Pressure (MAP) at 20, 60, 150, 180, and 240 minutes ($p<0.05$). The total duration of analgesia was similar in both groups (Group B: 3.91 hrs; Group L: 4.2 hrs; p=0.38). No significant sedation or adverse effects were observed in either group.

Conclusion: Hyperbaric levobupivacaine with intrathecal midazolam provides an effective anaesthetic block for lower limb surgery with superior hemodynamic stability compared to racemic bupivacaine. While bupivacaine offers a marginally faster sensory onset, levobupivacaine is a safer alternative for maintaining cardiovascular consistency while providing equivalent postoperative analgesia.

Keywords: Hyperbaric Levobupivacaine, Bupivacaine, Intrathecal Midazolam, Spinal Anaesthesia, Hemodynamic Stability, Lower Limb Surgery.

INTRODUCTION

Spinal anaesthesia achieves its clinical effect through a combination of sympathetic, sensory, and motor blockade by disrupting nerve transmission at the spinal nerve roots and dorsal root ganglia within the subarachnoid space. The physiological consequences of this blockade are widespread, affecting the cardiovascular system through sympathectomy-induced hypotension and bradycardia, and the gastrointestinal system through splanchnic innervation disruption. Racemic bupivacaine remains the most frequently utilized agent for spinal anaesthesia due to its potent, long-acting properties.

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However, its equimolar mixture of dextro- and levo-enantiomers carries a narrow therapeutic index, particularly regarding cardiotoxicity and hemodynamic instability. Levobupivacaine, the pure S(-) enantiomer of bupivacaine, has emerged as a safer alternative. It exhibits a lower affinity for cardiac sodium channels and greater plasma protein binding, thereby reducing the risk of fatal arrhythmias while providing comparable sensory blockade and potentially faster motor recovery.

To further optimize the quality of neuraxial blockade, various adjuvants—including opioids, alpha-2 agonists, and vasoconstrictors—are often combined with local anaesthetics. Recently, midazolam, a water-soluble benzodiazepine, has gained attention as an intrathecal adjuvant. By acting on gamma-aminobutyric acid (GABA) receptors within the spinal cord, midazolam has been shown to potentiate analgesia and prolong the duration of sensory and motor blocks without the significant

respiratory depression or neurotoxicity often associated with other adjuvants.

Despite the theoretical advantages of levobupivacaine and the analgesic benefits of midazolam, there remains a need for robust comparative data regarding their combined efficacy in clinical settings. This study aims to compare the quality of anaesthesia provided by intrathecal hyperbaric bupivacaine and hyperbaric levobupivacaine, each using preservative-free midazolam as an adjuvant, in patients undergoing lower limb surgeries. By evaluating block onset, duration, and hemodynamic stability, we seek to identify a more cardio-stable and efficacious regimen for regional anaesthesia.

MATERIALS AND METHODS

Study Design and Population

After obtaining approval from the Institutional Ethics Committee and securing written informed consent from all participants, this prospective, randomized, double-blind study was conducted. We enrolled patients aged 15–75 years, classified as American Society of Anesthesiologists (ASA) physical status I and II, who were scheduled for elective lower limb surgeries with an anticipated duration of less than 120 minutes.

Exclusion criteria included:

- Patient refusal or history of allergy to amide-type local anaesthetics or benzodiazepines.
- Height <150 cm or Body Mass Index (BMI) >35 kg/m².
- Contraindications to neuraxial blockade (e.g., coagulopathy, localized infection).

Any patient initially enrolled but requiring conversion to general anaesthesia on the day of surgery was designated as a drop-out and excluded from the final analysis.

Statistical Analysis

The sample size was chosen so as to maintain the overall alpha error <0.05 and power (1−beta) >0.9 and to provide useful additional safety and tolerability data. Data are presented as median (range), mean (SD), or frequencies as appropriate. Binomial data were compared using χ^2 or Fisher's test. Block characteristics were compared using the Kruskal–Wallis one-way analysis. In the event of a significant difference, post hoc comparisons were performed using the two-tailed Mann–Whitney U-test with a Bonferroni correction for multiple two-way testing. A P-value of <0.0167 was considered statistically significant. Data were analysed using a standard computer- based statistics package (Stats Direct statistical software version 2.5.)

Randomization and Blinding

Patients were randomly allocated into two equal groups using computer-generated random numbers. Group assignment was concealed using the sequentially numbered, sealed opaque envelope technique. To ensure blinding, the study drug was prepared by an anaesthesiologist not involved in the observation phase and handed to a second anaesthesiologist, blinded to the drug's identity, who performed the block and recorded the data.

- Group B: Received 2.8 ml of 0.5% hyperbaric bupivacaine (Anawin™) + 1 mg (0.2 ml) preservative-free midazolam.
- Group L: Received 2.8 ml of 0.5% hyperbaric levobupivacaine (Levoanawin™) + 1 mg (0.2 ml) preservative-free midazolam.

Anaesthetic Procedure

All patients underwent a standardized preoperative evaluation and followed fasting guidelines (8 hours for solids, 2 hours for clear fluids). In the operating theatre, standard monitoring was established. An 18G intravenous (IV) cannula was secured, and patients were preloaded with 10 ml/kg of Ringer's Lactate over 15–20 minutes.

Spinal anaesthesia was performed in the sitting position at the L3-L4 interspace using a 25G Quinke needle under strict aseptic conditions. Following the confirmation of free cerebrospinal fluid (CSF) flow, the study medication was injected, and the patient was immediately placed in the supine position.

Intraoperative Observations

Sensory blockade was assessed via pinprick using an 18G blunt needle at the midline every 2 minutes for the first 10 minutes, or until a T10 dermatome level was achieved. Motor blockade was evaluated using the Modified Bromage Scale:

Hemodynamic variables were recorded at baseline, every 5 minutes for the first 30 minutes, and subsequently every 30 minutes for 6 hours. Hypotension (defined as a >10% decrease from baseline MAP) was treated with a 200 ml fluid bolus or 6 mg IV mephentermine. Bradycardia (HR <10% from baseline/unstable) was treated with 0.6 mg IV atropine. Sedation levels were assessed at the end of surgery using the Observer's Assessment of Alertness/Sedation (OAA/S) Scale (Scores 0–5).

Postoperative Monitoring and Analgesia

In the Post-Anaesthesia Care Unit (PACU), sensory and motor levels were checked every 10 minutes until full recovery (Bromage 0). Postoperative pain was assessed using the Visual Analogue Scale (VAS).

- Total Duration of Analgesia: Defined as the interval between intrathecal injection and the first request for rescue analgesia.
- Rescue Analgesia**:** Provided via IV tramadol (1–2 mg/kg).

Patients were monitored for 24 hours for complications, including nausea, vomiting, pruritus, urinary retention, headache, or backache.

RESULT

Demographic Profile

The demographic analysis **(Table1)** revealed that the majority of patients in Group B were in the younger age (15–35 years, n=21, 70%), whereas Group L showed a more distributed age range, with 43.33% (n=13) in the 15–35 age group and 33.33% (n=10) in the 56–75 age group.

The mean age was 34.46 ± SD years in Group B and 41.8 ± SD years in Group L. Although Group L trended toward an older population, the difference was not statistically significant (p = 0.1), indicating that the two groups were comparable regarding age distribution for the purpose of this study.

Table 1: Comparison of Age Distribution between Two Groups

Age Distribution (in years)	Group B		Group L	
	No. of patients	Percentage	No. of patients	Percentage
15-35	21	70.00	13	43.33
36-55	4	13.33	7	23.33
56-75	5	16.67	10	33.33
Total	30	100.00	30	100.00
Mean±SD	34.46±16.94		41.8±17.32	
P-value	0.1			

Gender Distribution

Both study groups were predominantly male. In Group B **(Table 2)**, 70% (n=21) of the participants were male and 30% (n=9) were female. Similarly, Group L consisted of 76.67% (n=23) males and 23.33% (n=7) females. Statistical analysis yielded a p-value of 0.55, confirming that there was no significant difference in gender distribution between the two groups, ensuring they were comparable for the study.

Table 2: Comparison of Gender Distribution Between two Groups

Gender Distribution	Group B		Group L		P-value
	No. of patients	Percentage	No. of patients	Percentage	
Female	9	30.00	7	23.3	0.55
Male	21	70.00	29	96.67	
Total	30	100.00	30	100.00	

Hemodynamic Stability: Mean Arterial Pressure (MAP)

Analysis of Mean Arterial Pressure (MAP) trends (**Table 3 and 4)** revealed that Group L (Levobupivacaine) maintained significantly higher hemodynamic stability compared to Group B (Bupivacaine) at several critical time intervals. A statistically significant difference in favor of Group L was first observed at the 20-minute mark (83.28 vs. 77.46 mmHg; p = 0.049).

This trend of superior pressure maintenance in Group L continued with high statistical significance at 60 minutes ($p < 0.0001$), as well as at the 150, 180, and 240-minute intervals ($p < 0.05$). No significant differences were observed at the 90, 300, or 360-minute marks ($p > 0.05$), indicating that while both drugs eventually equilibrated, levobupivacaine provided a more stable MAP profile during the active surgical and early recovery phases.

Table 3: Comparison of Intra-op MAP between two groups (mmHg)

Intra-op MAP	Group B		Group L		P-value
	Mean	SD	Mean	SD	
at baseline	95.81	10.12	89.1	15.04	0.09
at 5 min	91.66	11.99	86.55	14.84	0.14
at 10 min	85.4	11.19	79.66	19.63	0.16
at 15 min	83.86	10.77	85.55	17.7	0.65
at 20 min	77.46	11.99	83.28	11.41	0.049
at 25 min	85.16	10.45	78.88	15.1	0.06
at 30 min	85	11.29	82.11	12	0.34
at 60 min	84.22	10.69	85.85	10.93	<0.0001
at 90 min	87.22	9.14	85	13.07	0.44
at 120 min	89.82	9.2	84	16.46	0.09

Table 4: Comparison of Post-op MAP between two groups (mmHg)

Post-op MAP	Group B		Group L		P-value
	Mean	SD	Mean	SD	
at 150 min	81.1	12.44	87.46	11.34	0.04
at 180 min	83.62	7.37	88.74	10.38	0.03
at 240 min	82.62	11.25	88.95	8.88	0.01
at 300 min	87.6	8.42	85	14.08	0.38
at 330 min	88.98	8.32	84.1	11.1	0.06
at 360 min	88.14	7.71	85.2	6.22	0.1

Sensory Block Characteristics

The onset of sensory blockade at the T10 dermatome **(Table 5)** was significantly faster in Group B compared to Group L. The mean time to reach T10 was 3.2 ± 0.9 minutes in the bupivacaine group, whereas the levobupivacaine group required 4.06 ±1.14 minutes. This difference was statistically significant (p = 0.002), indicating a more rapid sensory onset with racemic bupivacaine when combined with midazolam.

Table 5: Comparison of onset of sensory block to T10 between two groups

Parameter	Group B		Group L		P- value
	Mean	SD	Mean	SD	
Time to Sensory block onset T10(In min)	3.2	0.92	4.06	1.14	0.002

Motor Block Characteristics

The mean time to reach a Modified Bromage Scale score of 3 **(Table 6)** was slightly shorter in Group B (4.69 ±SD minutes) compared to Group L (5.00 ± SD minutes). However, this difference was not statistically significant, with a p-value of 0.36. These results suggest that the choice between hyperbaric bupivacaine and levobupivacaine, when supplemented with midazolam, does not significantly influence the speed of motor block onset.

Table 6: Comparison of Time for achievement of Modified Broamge Scale 3

Parameter	Group 1B		Group 1L		P-value
	Mean	SD	Mean	SD	
Onset of motor block (In min.)	4.69	0.75	5	1.71	0.36

Duration of Motor Blockade

The analysis of motor block regression (time to achieve a Modified Bromage Scale score of 0) **(Table 7)** showed no significant difference between the two study agents. The majority of patients in both Group B (83.33%) and Group L (93.33%) experienced a motor blockade duration lasting between 2.1 and 4 hours. Only a small fraction of patients (6.67% in each group) exhibited a prolonged blockade exceeding 4 hours.

The mean duration of motor blockade was 3.21 ± 0.73 hours in Group B and 3.2 ± 0.61 hours in Group L. Statistical comparison yielded a p-value of 0.95, confirming that the choice of local anaesthetic did not significantly impact the total duration of motor paralysis when using midazolam as an adjuvant.

Table 7: Comparison of Duration of motor blockade between two groups

Duration of Anesthesia (In hrs.)	Group B		Group L	
	No. of Patients	Percentage	No. of Patients	Percentage
≤2	3	10.00	0	0.00
2.1-4	25	83.33	28	93.33
4.1-6	2	6.67	2	6.67
Total	30	100.00	30	100.00
Mean±SD	3.21±0.73		3.2±0.61	
P-Value	0.95			

Total Duration of Analgesia

The total duration of analgesia **(Table 8)** was comparable between both study groups. The majority of participants in Group B (70%) and Group L (73.33%) maintained effective pain relief for 2.1 to 4 hours. A similar distribution was noted

for prolonged analgesia (4.1–6 hours), occurring in 26.67% of patients in both cohorts.

The mean duration of effective analgesia was 3.91 ± 1.39 hours in Group B and 4.2 ±1.18 hours in Group L. While the levobupivacaine group showed a slightly longer mean duration, the difference was not statistically significant (p = 0.38). These findings indicate that hyperbaric levobupivacaine and bupivacaine provide nearly identical durations of postoperative pain relief when combined with 1 mg of intrathecal midazolam.

Table 8: Comparison of Duration of Effective Analgesia between two groups

Duration of Effective Analgesia (In hrs)	Group B		Group L	
	No. of Patients	Percentage	No. of Patients	Percentage
≤2	1	3.33	0	0.00
2.1-4	21	70.00	22	73.33
4.1-6	8	26.67	8	26.67
Total	30	100.00	30	100.00
Mean±SD	3.91±1.39		4.2±1.18	
P-Value	0.38			

Sedation Levels (OAA/S Scale)

Sedation levels, assessed using the Observer's Assessment of Alertness/Sedation (OAA/S) scale **(Table 9)**, were comparable between both cohorts at the conclusion of the surgery. In Group B, 60% of patients were fully awake (Scale 5), while 40% responded lethargically to their name (Scale 4). Similarly, in Group L, 53.33% of patients were at Scale 5 and 46.67% at Scale 4.

The mean sedation score for Group B was 4.6 ± 0.49 compared to 4.5 ± 0.50 in Group L. The p-value of 0.43 indicates that the difference in sedation between hyperbaric bupivacaine and levobupivacaine, when each is administered with 1 mg of intrathecal midazolam, is not statistically significant. This suggests that the choice of local anaesthetic does not influence the sedative effects of the adjuvant.

Table 9: Comparison of Sedation Scale between two groups at the end of surgery

Sedation Scale	Group B		Group L	
	No. of patients	Percentage	No. of patients	Percentage
Four	12	40.00	14	46.67
Five	18	60.00	16	53.33
Total	30	100.00	30	100.00
Mean±SD	4.6±0.49		4.5±0.50	
P-value	0.43			

Adverse Effects and Safety Profile

Clinical monitoring for postoperative complications **(Table 10)** revealed an excellent safety profile for both study regimens. There was no incidence (0%) of adverse effects, such as nausea, vomiting, pruritus, urinary retention, post-dural puncture headache (PDPH), or neurological deficits, in either Group B or Group L.

Table 10: Comparison of Adverse effects between two groups

Adverse Effects	Group B		Group L		P- value
	No. of Patients	Percentage	No. of Patients	Percentage	
Nausea	0	0.00	0	0.00	-
Vomiting	0	0.00	0	0.00	-
Headache	0	0.00	0	0.00	-
Dizziness	0	0.00	0	0.00	-
Shivering	0	0.00	0	0.00	-

DISCUSSION

The primary objective of this study was to compare the clinical efficacy and safety of hyperbaric bupivacaine and hyperbaric levobupivacaine, each supplemented with 1 mg of preservative-free midazolam, for spinal anaesthesia in lower limb surgeries. Our findings suggest that while both agents provide adequate surgical anaesthesia, hyperbaric levobupivacaine offers a superior hemodynamic profile, whereas racemic bupivacaine exhibits a marginally faster sensory onset.

Sensory and Motor Block Characteristics

In our study, the mean time for sensory block onset to the T10 level was significantly faster in Group B (3.2 minutes) compared to Group L (4.06 minutes) (p=0.002). This finding is consistent with the observations of Piacherski et al.(1), who reported that hyperbaric bupivacaine achieves a complete sensory block faster than levobupivacaine. The slightly delayed onset in Group L may be attributed to the lower clinical potency of the S(-) enantiomer compared to the racemic mixture, as suggested by Burlacu et al.(2) Regarding motor blockade, the onset times were comparable between Group B (4.69 min) and Group L (5.00 min) (p=0.36). Similarly, the total duration of motor blockade showed no significant difference (p=0.95), with both groups averaging approximately 3.2 hours. While Erbay et al.(3) observed faster recovery times to Bromage Score Zero with levobupivacaine, their use of lower dosages (7.5 mg) compared to our study (14 mg) likely accounts for this discrepancy. Our results suggest that at higher clinical doses, the motor block characteristics of both drugs equilibrate.

Hemodynamic Stability

A critical finding of this study was the enhanced cardiovascular stability provided by levobupivacaine. Group L exhibited significantly higher Mean Arterial Pressure (MAP) values at several intervals, most notably at 20 and 60 minutes intraoperatively ($p < 0.05$). This superior stability supports the claims of Gulec et al.(4) and Singh et al.(5), who recommended levobupivacaine for its reduced cardiotoxicity and more predictable drug spread. The reduced affinity of levobupivacaine for cardiac sodium channels likely contributes to this dampened sympathetic response compared to the racemic isomer.

Role of Intrathecal Midazolam

The addition of 1 mg of midazolam as an adjuvant served to prolong the duration of analgesia without increasing the incidence of side effects. Our results showed a mean duration of effective analgesia of 3.91 hours in Group B and 4.2 hours in Group L (p=0.38). These findings align with Hung et al.(6) and Bharti et al.(7), who concluded that intrathecal midazolam potentiates the analgesic effect of local anaesthetics by acting on GABA receptors in the spinal cord.

Notably, we observed no incidence of nausea, vomiting, or significant sedation. While Nayak et al.(8) reported higher sedation levels with midazolam, they utilized a higher dose (2.5 mg); our study suggests that a 1 mg dose provides sufficient analgesia while maintaining a high level of patient alertness (OAA/S scale of 4–5).

CONCLUSION

The combination of hyperbaric levobupivacaine and midazolam provides a robust and reliable anaesthetic alternative for lower limb surgeries. While racemic bupivacaine offers a slightly faster sensory onset, levobupivacaine's predictable spread and superior hemodynamic profile make it a safer choice, particularly for patients where blood pressure maintenance is critical.

By utilizing midazolam as an adjuvant, clinicians can achieve prolonged postoperative analgesia and stable motor recovery, facilitating early, painless mobilization and potentially reducing the risk of complications such as deep vein thrombosis. We recommend further large-scale trials to optimize age-specific dosing protocols and evaluate long-term neurological safety.

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