e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(7); 160-167

Original Research Article

A Study to Compare the Effects of Intrathecal Midazolam and Intrathecal Buprenorphine as Adjuvant to Levobupivacaine Heavy in Spinal Anaesthesia

Prabuddha Bhave[1], Gajendra Singh[2], Deepika V. K.[3], Sai Vijayashree[4], Indira[5]

[1]Postgraduate, M R Medical College, Kalaburagi, Karnataka, India
[2]Professor, Department of Anaesthesiology, M R Medical College, Kalaburagi, Karnataka, India
[3]Postgraduate, M R Medical College, Kalaburagi, Karnataka, India
[4]Postgraduate, M R Medical College, Kalaburagi, Karnataka, India
[5]Postgraduate, M R Medical College, Kalaburagi, Karnataka, India

Received: 01-04-2026 / Revised: 15-05-2026 / Accepted: 21-06-2026
Corresponding author: Dr. Gajendra Singh
Conflict of interest: Nil

Abstract

Background: Intrathecal adjuvants are commonly added to local anaesthetics during spinal anaesthesia to improve block characteristics and prolong postoperative analgesia. Midazolam and buprenorphine are two such adjuvants with distinct mechanisms of action and analgesic profiles. The present study compared the efficacy and safety of intrathecal midazolam and intrathecal buprenorphine when used as adjuvants to hyperbaric levobupivacaine in patients undergoing infraumbilical surgeries.

Methods: This prospective interventional study was conducted in 60 patients aged 18–60 years with ASA physical status I or II undergoing elective infraumbilical surgeries under spinal anaesthesia. Patients were randomly allocated into two groups of 30 each. Group A received intrathecal midazolam 2 mg with 0.5% hyperbaric levobupivacaine, while Group B received intrathecal buprenorphine 120 µg with 0.5% hyperbaric levobupivacaine. Sensory and motor block characteristics, duration of postoperative analgesia, haemodynamic parameters, visual analogue scale (VAS) scores, sedation scores, and adverse effects were evaluated.

Results: Baseline demographic and clinical characteristics were comparable between the groups. Sensory onset was significantly faster in Group A (3.82 ± 0.93 min) than Group B (4.20 ± 1.58 min; p = 0.009). However, Group B demonstrated significantly prolonged two-segment sensory regression (210.83 ± 41.23 vs. 150.53 ± 32.82 min; p = 0.010), longer motor block duration (175.97 ± 40.23 vs. 143.33 ± 36.41 min; p = 0.033), and markedly prolonged postoperative analgesia (602.00 ± 128.99 vs. 307.67 ± 103.38 min; p = 0.005). VAS pain scores were significantly lower and Ramsay sedation scores significantly higher in Group B throughout the postoperative period. The incidence of hypotension, bradycardia, nausea, and vomiting was comparable between the groups.

Conclusion: Both intrathecal midazolam and buprenorphine were effective adjuvants to hyperbaric levobupivacaine for spinal anaesthesia. Midazolam provided a faster onset of sensory blockade, whereas buprenorphine produced significantly longer sensory and motor blockade, superior postoperative analgesia, and lower postoperative pain scores without increasing adverse effects. Intrathecal buprenorphine may therefore be the preferred adjuvant when prolonged postoperative analgesia is desired.

Keywords: Spinal Anaesthesia, Levobupivacaine, Intrathecal Midazolam, Intrathecal Buprenorphine, Postoperative Analgesia, Sensory Block, Motor Block, Adjuvant.

DOI: 10.25258/ijcpr.18.7.26

Introduction

Spinal anaesthesia is one of the most commonly employed regional anaesthetic techniques for infraumbilical surgical procedures owing to its rapid onset, dense sensory and motor blockade, ease of administration, and reduced perioperative morbidity compared with general anaesthesia [1]. Despite these advantages, the clinical utility of spinal anaesthesia is often constrained by the limited duration of action of local anaesthetic agents and the occurrence of haemodynamic disturbances resulting from sympathetic blockade, particularly during prolonged surgical procedures [2]. Consequently, considerable attention has been directed toward identifying suitable local

anaesthetics and intrathecal adjuvants that can enhance block quality, prolong postoperative analgesia, and maintain haemodynamic stability. Levobupivacaine, the pure S(-)-enantiomer of bupivacaine, has emerged as an attractive alternative to racemic bupivacaine because of its favourable pharmacological and safety profile [3]. Hyperbaric levobupivacaine provides reliable sensory and motor blockade with improved predictability of spread within the subarachnoid space while demonstrating less cardiotoxicity and neurotoxicity than racemic bupivacaine [4].

The reduced affinity of levobupivacaine for myocardial sodium channels lowers the risk of arrhythmias and cardiac depression, thereby contributing to greater cardiovascular safety [5]. However, although hyperbaric levobupivacaine provides effective anaesthesia for infraumbilical surgeries, the duration of postoperative analgesia remains suboptimal, necessitating the use of adjuvant agents to improve analgesic outcomes. Intrathecal adjuvants are frequently added to local anaesthetics to enhance the quality and duration of spinal anaesthesia.

These agents can prolong sensory blockade, improve postoperative pain relief, reduce the requirement for rescue analgesics, and decrease the total dose of local anaesthetic needed [6]. Among the various adjuvants available, opioids continue to be widely used because of their potent analgesic effects mediated through spinal opioid receptors. Buprenorphine, a highly lipophilic partial μ-opioid receptor agonist and κ-receptor antagonist, has gained considerable interest as an intrathecal adjuvant [7].

Owing to its strong receptor affinity and slow dissociation from opioid receptors, buprenorphine provides prolonged spinal analgesia and is approximately 25–30 times more potent than morphine [8]. Furthermore, its high lipid solubility limits cephalad spread within the cerebrospinal fluid, reducing the risk of delayed respiratory depression while providing effective postoperative analgesia with a relatively low incidence of opioid-related adverse effects [9,10].

Midazolam represents an alternative non-opioid intrathecal adjuvant with a distinct mechanism of action. It exerts antinociceptive effects through gamma-aminobutyric acid (GABA-A) receptors located in the dorsal horn of the spinal cord, particularly within lamina II, an area involved in nociceptive signal processing [11,12]. By enhancing inhibitory neurotransmission and suppressing nociceptive pathways, intrathecal midazolam has been shown to prolong postoperative analgesia and improve block characteristics without producing the common adverse effects associated with opioids, such as pruritus, nausea, vomiting, and respiratory depression [13]. Additionally, midazolam possesses anxiolytic properties and exhibits minimal haemodynamic effects, making it a potentially valuable adjunct in spinal anaesthesia [14].

Although both buprenorphine and midazolam have demonstrated efficacy as intrathecal adjuvants, evidence directly comparing their performance when combined with hyperbaric levobupivacaine remains limited. Given their differing mechanisms of action and side-effect profiles, a comparative evaluation is clinically important. The present study was therefore undertaken to compare intrathecal buprenorphine and midazolam as adjuvants to hyperbaric levobupivacaine.

Materials and Methods

The present study was conducted as a prospective interventional comparative study to evaluate and compare the effects of intrathecal midazolam and intrathecal buprenorphine as adjuvants to 0.5% hyperbaric levobupivacaine for spinal anaesthesia.

Eligible participants were randomly allocated into two parallel groups receiving one of the study drug combinations. Uniform anaesthetic techniques, perioperative management, and postoperative assessments were followed throughout the study to facilitate valid comparison between the two groups. The study included adult patients scheduled for elective abdominal and infraumbilical surgeries under subarachnoid block.

Inclusion Criteria

Patients fulfilling the following criteria were included:

1. Patients willing to provide written informed consent.
2. Patients aged between 18 and 60 years.
3. Patients belonging to American Society of Anesthesiologists (ASA) physical status Grade I or II.
4. Patients scheduled for elective abdominal or infraumbilical surgeries under spinal anaesthesia.

Exclusion Criteria

Patients meeting any of the following criteria were excluded:

1. ASA physical status Grade III or IV.
2. Presence of significant neurological, cardiovascular, respiratory, renal, or hepatic disease.
3. History of hypersensitivity to local anaesthetics, benzodiazepines, or opioids.
4. Absolute contraindications to spinal anaesthesia.

Study Groups: The enrolled participants were divided into two equal groups:

Group A (n = 30): Patients received intrathecal 0.5% hyperbaric levobupivacaine 2.8 mL combined with preservative-free midazolam 2 mg (0.4 mL), making a total intrathecal volume of 3.2 mL.

Group B (n = 30): Patients received intrathecal 0.5% hyperbaric levobupivacaine 2.8 mL combined with preservative-free buprenorphine 120 µg (0.4 mL), making a total intrathecal volume of 3.2 mL.

Study Parameters: The following parameters were evaluated:

Primary Parameters

- Onset time of sensory blockade (time required to achieve T10 sensory level).
- Maximum sensory level attained.
- Duration of sensory blockade (time to two-segment regression).
- Onset time of motor blockade (time required to achieve Bromage Grade III).
- Duration of motor blockade (time from Bromage Grade III to Bromage Grade 0).
- Duration of postoperative analgesia.

Secondary Parameters

- Intraoperative haemodynamic variables including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and peripheral oxygen saturation (SpO_2).
- Incidence of adverse effects such as hypotension, nausea, vomiting, tachycardia, respiratory depression, and other complications.

Study Procedure: All patients underwent a detailed pre-anaesthetic evaluation on the day preceding surgery. Patients were instructed to remain fasting for at least 6 hours for solid foods and 2 hours for clear liquids. Baseline vital parameters were recorded, and an 18-gauge intravenous cannula was secured. Inside the operating theatre, standard monitoring including electrocardiography, non-invasive blood pressure, and pulse oximetry was instituted.

Under strict aseptic precautions, spinal anaesthesia was administered in the left lateral position at the L3–L4 intervertebral space using a 25-gauge Quincke spinal needle.

Following confirmation of free cerebrospinal fluid flow, the allocated study drug solution was injected intrathecally. Patients were subsequently positioned supine. Sensory blockade was assessed using a pin-prick method, while motor blockade was evaluated using the Modified Bromage Scale. Haemodynamic parameters were monitored continuously throughout the intraoperative period.

Data Collection: All observations were documented in a predesigned data collection proforma. Parameters including sensory and motor block characteristics, duration of postoperative analgesia, haemodynamic changes, and adverse events were recorded from the time of intrathecal drug administration until complete recovery of motor function.

Statistical Analysis: The collected data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 25.0. Quantitative variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Comparisons between the two groups were performed using the unpaired Student's t-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: Prior approval for the study was obtained from the Institutional Ethics Committee before commencement of patient recruitment. Written informed consent was obtained from all participants in their local language after explaining the nature and purpose of the study. Confidentiality of patient information was maintained throughout the study. No additional risk beyond routine anaesthetic management was imposed on participants, and all patients were monitored closely to ensure perioperative safety.

Results and Analysis

The baseline demographic and clinical characteristics of the study participants are presented in Table 1 and Figure 1. Sex distribution was comparable between the two groups, with females constituting 56.7% of Group A and 36.7% of Group B ($p = 0.121$). Most patients in both groups belonged to ASA Grade I, accounting for 93.3% and 90.0% in Groups A and B, respectively ($p = 0.640$). Anthropometric parameters including height, weight, and BMI were also similar between the groups, with no statistically significant differences observed ($p > 0.05$ for all variables). These findings indicate that the two groups were comparable at baseline (Table 1, Figure 1).

The comparison of surgical characteristics and perioperative adverse events is shown in Table 2. The mean duration of surgery was 74.47 ± 24.50 minutes in Group A and 72.03 ± 22.86 minutes in Group B, showing a statistically significant difference ($p = 0.033$). Hypotension occurred in 16.7% of patients in Group A and 6.7% in Group B, while bradycardia was observed in 50.0% and 60.0% of patients, respectively. Nausea and vomiting were infrequent in both groups. However,

none of the adverse events differed significantly between the groups ($p > 0.05$) (Table 2).

The characteristics of sensory and motor blockade are summarized in Table 3 and illustrated in Figure 2. Sensory onset was significantly faster in Group A compared to Group B (3.82 ± 0.93 vs. 4.20 ± 1.58 minutes, $p = 0.009$). Similarly, the time required to achieve the maximum sensory level was shorter in Group A ($p = 0.024$). In contrast, two-segment sensory regression was significantly prolonged in Group B (210.83 ± 41.23 minutes) compared to Group A (150.53 ± 32.82 minutes) ($p = 0.010$). Motor block onset was slightly faster in Group B ($p = 0.042$), and the duration of motor block was significantly longer in Group B than in Group A (175.97 ± 40.23 vs. 143.33 ± 36.41 minutes, $p = 0.033$). Peak motor blockade was identical in both groups (Table 3, Figure 2). Postoperative analgesia outcomes are presented in Table 4. Group B demonstrated a significantly longer duration of analgesia compared with Group A (602.00 ± 128.99 vs. 307.67 ± 103.38 minutes, $p = 0.005$). Similarly, the time to first rescue analgesic requirement was significantly prolonged in Group B ($p = 0.005$). These findings indicate superior postoperative analgesic efficacy of intrathecal buprenorphine compared with intrathecal midazolam (Table 4).

The comparison of postoperative pain intensity measured using the Visual Analogue Scale (VAS) is shown in Table 5. Pain scores were consistently lower in Group B at all postoperative time intervals. Significant differences were observed at 1 hour ($p = 0.021$), 2 hours ($p = 0.018$), 4 hours ($p = 0.006$), 6 hours ($p = 0.002$), 8 hours ($p = 0.001$), 12 hours ($p = 0.003$), and 24 hours ($p = 0.045$). Group A exhibited progressively increasing pain scores up to 12 hours postoperatively, whereas Group B maintained lower scores throughout the observation period, indicating more effective and prolonged analgesia (Table 5).

Sedation profiles assessed using the Ramsay Sedation Scale are presented in Table 6. Baseline sedation scores were identical in both groups. However, Group B demonstrated significantly higher sedation scores from 5 minutes onward.

Statistically significant differences were observed at 5 minutes ($p = 0.012$), 10 minutes ($p = 0.001$), 15 minutes ($p = 0.001$), 30 minutes ($p = 0.002$), 60 minutes ($p = 0.003$), and 120 minutes ($p = 0.005$). Although sedation scores gradually declined after reaching a peak at approximately 30 minutes, Group B consistently maintained higher scores throughout the observation period, indicating superior sedative effects (Table 6).

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Group A (n=30)	Group B (n=30)	p-value
Female, n (%)	17 (56.7)	11 (36.7)	0.121
Male, n (%)	13 (43.3)	19 (63.3)	
ASA I, n (%)	28 (93.3)	27 (90.0)	0.640
ASA II, n (%)	2 (6.7)	3 (10.0)	
Height (cm), Mean ± SD	164.23 ± 6.78	166.37 ± 8.39	0.296
Weight (kg), Mean ± SD	70.17 ± 13.01	71.33 ± 9.58	0.183
BMI (kg/m²), Mean ± SD	25.94 ± 4.31	25.84 ± 3.48	0.674

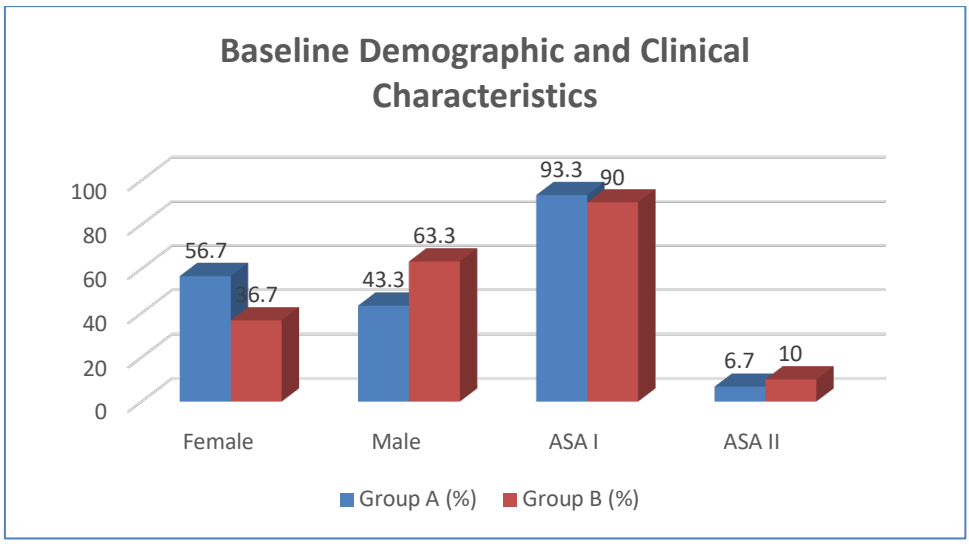

Figure 1: Baseline Demographic and Clinical Characteristics

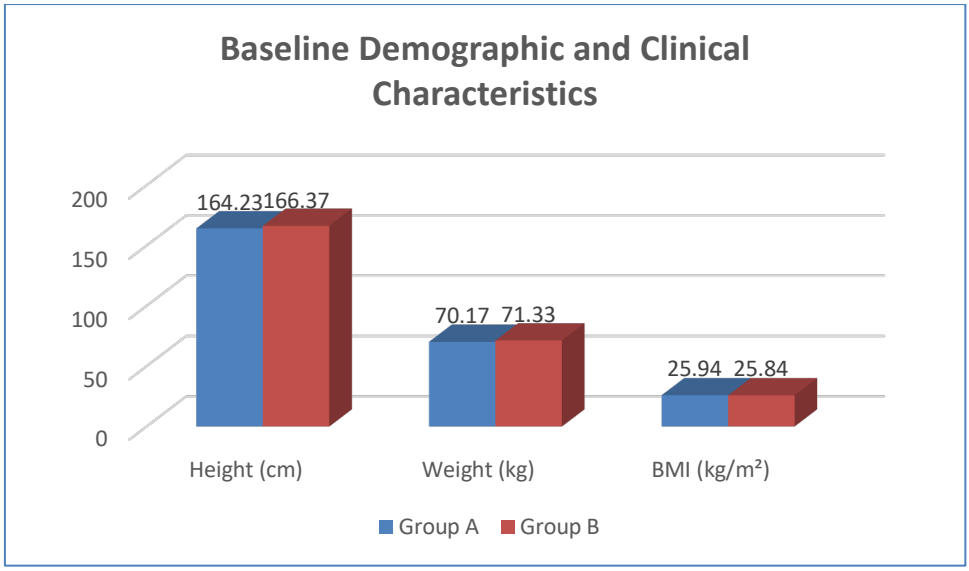

Figure 2: Baseline Demographic and Clinical Characteristics

Table 2: Surgical Characteristics and Adverse Events

Variable	Group A (n=30)	Group B (n=30)	p-value
Surgery duration (min), Mean ± SD	74.47 ± 24.50	72.03 ± 22.86	0.033*
Hypotension, n (%)	5 (16.7)	2 (6.7)	0.228
Bradycardia, n (%)	15 (50.0)	18 (60.0)	0.436
Nausea/Vomiting, n (%)	4 (13.3)	3 (10.0)	0.688

Table 3: Sensory and Motor Block Characteristics

Variable	Group A Mean ± SD	Group B Mean ± SD	p-value
Sensory onset (min)	3.82 ± 0.93	4.20 ± 1.58	0.009*
Time to maximum sensory level (min)	7.36 ± 1.50	7.58 ± 1.93	0.024*
Two-segment regression (min)	150.53 ± 32.82	210.83 ± 41.23	0.010*
Motor onset to Bromage 3 (min)	6.23 ± 1.90	5.88 ± 1.32	0.042*
Motor block duration (min)	143.33 ± 36.41	175.97 ± 40.23	0.033*
Peak Bromage score	3.00 ± 0.00	3.00 ± 0.00	—

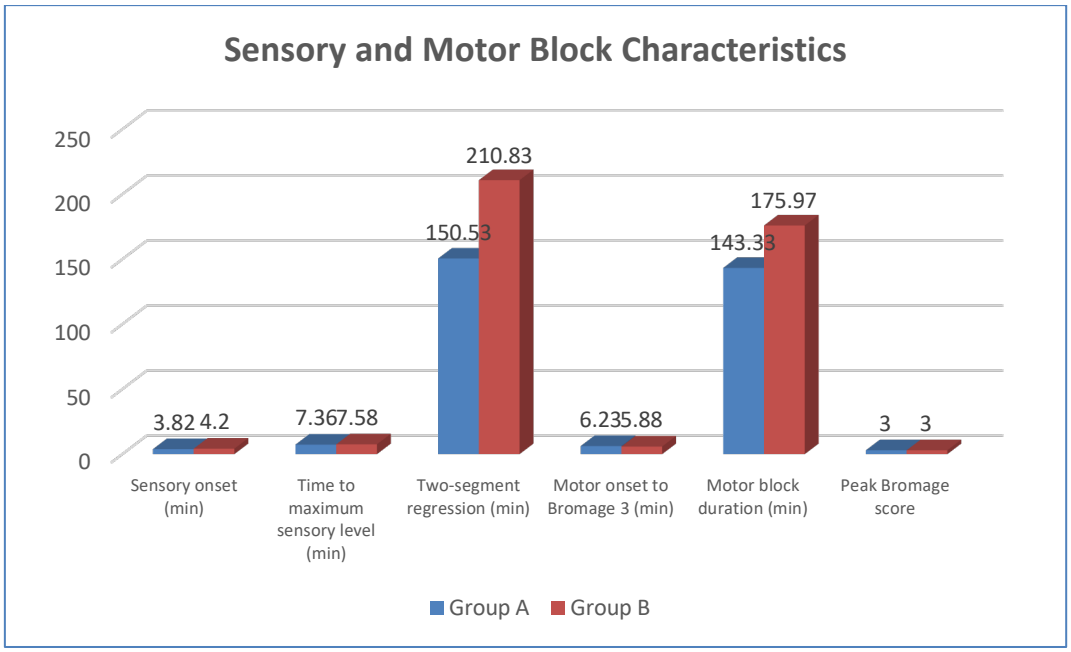

Figure 3: Sensory and Motor Block Characteristics

Table 4: Postoperative Analgesia Characteristics

Variable	Group A Mean ± SD	Group B Mean ± SD	p-value
Duration of analgesia (min)	307.67 ± 103.38	602.00 ± 128.99	0.005*
Time to first analgesic requirement (min)	307.67 ± 103.38	602.00 ± 128.99	0.005*

Table 5: Comparison of VAS Pain Scores

Time Interval	Group A Mean ± SD	Group B Mean ± SD	p-value
1 hour	1.2 ± 0.5	0.8 ± 0.4	0.021*
2 hours	2.1 ± 0.7	1.5 ± 0.6	0.018*
4 hours	3.5 ± 0.9	2.4 ± 0.8	0.006*
6 hours	4.8 ± 1.1	3.2 ± 1.0	0.002*
8 hours	5.6 ± 1.2	3.8 ± 1.1	0.001*
12 hours	6.2 ± 1.3	4.5 ± 1.2	0.003*
24 hours	3.9 ± 1.0	3.2 ± 0.9	0.045*

Table 6: Comparison of Ramsay Sedation Scores

Time Interval	Group A Mean ± SD	Group B Mean ± SD	p-value
Baseline	2.00 ± 0.00	2.00 ± 0.00	—
5 min	2.10 ± 0.30	2.40 ± 0.50	0.012*
10 min	2.20 ± 0.40	2.80 ± 0.60	0.001*
15 min	2.30 ± 0.50	3.00 ± 0.70	0.001*
30 min	2.40 ± 0.50	3.10 ± 0.80	0.002*
60 min	2.30 ± 0.50	3.00 ± 0.70	0.003*
120 min	2.20 ± 0.40	2.80 ± 0.60	0.005*

P < 0.05 considered statistically significant

Discussion

The present prospective interventional study compared intrathecal midazolam and intrathecal buprenorphine as adjuvants to hyperbaric levobupivacaine in patients undergoing infraumbilical surgeries under spinal anaesthesia. The study demonstrated that while intrathecal midazolam produced a slightly faster onset of sensory blockade, intrathecal buprenorphine significantly prolonged sensory and motor block duration, postoperative analgesia, and improved postoperative pain control without increasing adverse effects.

Baseline demographic and surgical characteristics were comparable between the groups. Most patients were ASA Grade I (93.3% in Group A and 90.0% in Group B), with similar BMI and duration of surgery, ensuring reliable comparison of anaesthetic outcomes. Similar demographic comparability has been reported by Shadangi et al. [15], Singh et al. [16], Lotliker [17], and Nayak et al. [18].

Haemodynamic stability was well maintained in both groups. Hypotension (16.7% vs 6.7%), bradycardia (50.0% vs 60.0%), and nausea/vomiting (13.3% vs 10.0%) showed no significant intergroup differences. These findings are in agreement with Singh et al. [16], who reported stable haemodynamics with intrathecal buprenorphine, and Elfawal et al. [19], who demonstrated minimal adverse effects with intrathecal midazolam. Fawaz et al. [20] also observed no significant increase in complications with intrathecal midazolam.

Sensory block onset was significantly faster with midazolam (3.82 ± 0.93 min) than buprenorphine (4.20 ± 1.58 min), and time to achieve maximum sensory level was also shorter. However, two-segment regression was significantly prolonged in the buprenorphine group (210.83 ± 41.23 min vs 150.53 ± 32.82 min). Shadangi et al. [15] reported prolonged sensory block with intrathecal midazolam compared with control, while Elfawal et al. [19] and Lotliker [17] also demonstrated delayed sensory regression with midazolam. Singh et al. [16] reported even greater prolongation of sensory blockade with buprenorphine, supporting the present findings.

Motor block onset was slightly faster with buprenorphine (5.88 ± 1.32 min) than midazolam (6.23 ± 1.90 min). Motor block duration was significantly longer in the buprenorphine group (175.97 ± 40.23 min vs 143.33 ± 36.41 min). Previous studies by Shadangi et al. [15] and Elfawal et al. [16] showed minimal influence of midazolam on motor block duration. Similar prolongation of motor blockade with opioid adjuvants has been reported by FRH CR [21].

The most important finding of the study was the marked prolongation of postoperative analgesia with buprenorphine. Duration of analgesia was significantly longer in Group B (602.00 ± 128.99 min) compared with Group A (307.67 ± 103.38 min). Singh et al. [16] similarly reported prolonged

postoperative analgesia with intrathecal buprenorphine. Although Shadangi et al. [15], Lotliker [17], and Elfawal et al. [19] demonstrated improved analgesia with intrathecal midazolam, the analgesic duration observed with buprenorphine in the present study was substantially greater.

Postoperative VAS scores remained significantly lower in the buprenorphine group at 6, 12, and 24 hours, indicating superior pain control. Ramsay sedation scores were also higher with buprenorphine, reflecting improved patient comfort without clinically significant respiratory depression. Similar findings have been reported in studies evaluating opioid-based intrathecal adjuvants.

Overall, both intrathecal midazolam and buprenorphine proved to be safe and effective adjuvants to hyperbaric levobupivacaine. Midazolam offered a faster sensory onset, whereas buprenorphine provided significantly prolonged sensory and motor blockade, superior postoperative analgesia, lower pain scores, and acceptable sedation. These findings favour intrathecal buprenorphine when prolonged postoperative analgesia is desired, while intrathecal midazolam may be preferred when rapid onset and earlier recovery are important.

Conclusion

Both intrathecal midazolam and intrathecal buprenorphine were effective adjuvants to hyperbaric levobupivacaine for spinal anaesthesia, providing satisfactory sensory and motor blockade with minimal adverse effects. Intrathecal midazolam was associated with a slightly faster onset of sensory block, whereas intrathecal buprenorphine produced significantly prolonged sensory blockade, motor blockade, and postoperative analgesia. Patients receiving buprenorphine also demonstrated lower postoperative pain scores and delayed requirement for rescue analgesia without an increase in complications. Therefore, intrathecal buprenorphine appears to be a superior adjuvant when prolonged postoperative pain relief is desired in infraumbilical surgeries.

Limitations

The present study was conducted at a single tertiary care centre with a relatively small sample size, which may limit the generalizability of the findings. The study included only ASA Grade I and II patients undergoing infraumbilical surgeries; therefore, the results may not be applicable to higher-risk patients or other surgical populations. Long-term postoperative outcomes and patient satisfaction were not evaluated. Additionally, only a single dose of each adjuvant was studied, precluding assessment of dose–response relationships.

Reference

1. Greene NM. Physiology of spinal anaesthesia. Baltimore: Williams & Wilkins; 1981.
2. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesth Analg. 1992;74(4):460-465.
3. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol. 2005;19(2):247-268.
4. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and clinical use. Drugs. 2000;59(3):551-579.
5. McLeod GA. Density of spinal anaesthetic solutions. Anaesthesia. 2004;59(9):922-926.
6. Yaksh TL, Rudy TA. Analgesia following spinal delivery of opioids. Pain. 1976;2(4):201-218.
7. Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627-632.
8. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81-110.
9. Singh P, Kumar A, Singh U, Bajwa SJ, Singh A. Comparative evaluation of intrathecal bupivacaine alone and in combination with buprenorphine or fentanyl for lower limb surgeries. J Anaesthesiol Clin Pharmacol. 2016;32(2):229-233.
10. Olofsson C, Nygårds EB, Biber B, Björkman S. Pharmacokinetics and analgesic effect of intrathecal and epidural bupivacaine in humans. Acta Anaesthesiol Scand. 1984;28(3):279-284.
11. Faull RL, Villiger JW. Benzodiazepine receptors in the human spinal cord: a detailed anatomical study. Neuroscience. 1987;20(2):597-609.
12. Woolf CJ, Chung JM. The use of experimentally induced polyneuropathy to analyze the mechanisms of chronic pain. Pain. 1982;12(4):347-365.
13. Shadangi BK, Acharya R, Singh S, Patel R. A prospective randomized study comparing the analgesic effect of intrathecal midazolam with fentanyl as adjuvant to bupivacaine. Singapore Med J. 2011;52(7):432-435.
14. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat: evidence for spinally mediated analgesia. Br J Anaesth. 1996;77(2):193-197.

15. Shadangi BK, Garg R, Pandey R, Das T. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study. Singapore Med J. 2011; 52(6): 432-436.
16. Singh AP, Kaur R, Gupta R, Kumari A. Intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries. J Anaesthesiol Clin Pharmacol. 2016; 32(2): 229-233.
17. Lotliker SD. A comparative evaluation of the analgesic efficacy of intrathecal midazolam as an adjuvant to 0.5% bupivacaine with a placebo as an adjuvant to 0.5% bupivacaine in patients undergoing infraumbilical surgeries [dissertation]. Bengaluru: Rajiv Gandhi University of Health Sciences; 2018.
18. Nayak A, Ninave S, Tayade S, Tayade H, Nayak Sr A. Intrathecal adjuvant midazolam versus fentanyl with hyperbaric bupivacaine for post-operative analgesia in women undergoing total abdominal hysterectomy. Cureus. 2023;15(6):e40518.
19. Elfawal SM, Shoukry AA, Nofal WH. Comparative study of intrathecal midazolam versus fentanyl as adjuvants to ropivacaine for lower-limb surgery. Ain Shams J Anaesthesiol. 2016; 9(3):348-354.
20. Fawaz AA, Elie TY, Abdelwahab WA, Mattar AA. Comparative study between intrathecal fentanyl and midazolam as adjuvant to local anesthetics in spinal anesthesia in elective cesarean section in post-operative anesthesia and post-operative analgesia. Ain Shams Med J. 2020;71(4):841-852.
21. FRH CR. Comparison of intrathecal dexmedetomidine and buprenorphine as adjuvant to bupivacaine for lower limb surgeries [dissertation]. Bengaluru: Rajiv Gandhi University of Health Sciences; 2019.