RESEARCH PAPER

Comparison Of Intrathecal Midazolam Versus Fentanyl As An Adjuvant To Bupivacaine For Postoperative Analgesia In Lower-Abdominal Surgeries Under Spinal Anaesthesia

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Abstract

Background: Intrathecal bupivacaine is widely used for spinal anaesthesia in lower abdominal surgeries. However, its limited postoperative analgesic duration necessitates the use of adjuvants. Among the various intrathecal adjuvants, fentanyl (a lipophilic opioid) and midazolam (a short-acting benzodiazepine with antinociceptive properties) are commonly used, though their comparative effectiveness and safety remain subjects of interest.

Aim: This study aimed to compare the efficacy and safety of intrathecal midazolam and fentanyl as adjuvants to hyperbaric bupivacaine (0.5%) in patients undergoing elective lower abdominal surgeries.

Methods: In this prospective, randomized, double-blind study, 140 ASA I/II patients aged 18–60 years scheduled for elective lower abdominal surgeries were assigned to two groups. Group A received 3 ml (15 mg) of 0.5% hyperbaric bupivacaine + 0.4 ml (2 mg) preservative-free midazolam, while Group B received 3 ml (15 mg) of 0.5% hyperbaric bupivacaine + 0.4 ml (20 µg) fentanyl intrathecally. Key outcomes assessed were onset and duration of sensory and motor blocks, duration of effective analgesia, need for rescue analgesia, hemodynamic changes, and adverse effects.

Results: Midazolam significantly prolonged the duration of sensory and motor block as well as effective analgesia compared to fentanyl ($p < 0.001$). The requirement for rescue analgesia was lower in the midazolam group. Hemodynamic parameters remained stable across both groups, though fentanyl was associated with a higher incidence of side effects such as pruritus and nausea.

Conclusion: Intrathecal midazolam is a safe and effective alternative to fentanyl as an adjuvant to bupivacaine in spinal anaesthesia, offering prolonged analgesia with fewer side effects.

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Introduction

In developing countries like India, the frequency of lower abdominal surgeries has been steadily rising, primarily due to an increasing number of gynecological and urological procedures performed in both elective and emergency settings [1]. For these surgeries, regional anaesthesia is often favored over general anaesthesia because of its multiple advantages. These include effective attenuation of the surgical stress response, reduced exposure to multiple drugs, minimization of airway-related complications, decreased incidence of postoperative nausea and vomiting, and superior postoperative pain control [2]. Among various regional anaesthetic techniques, spinal anaesthesia is the most commonly employed for lower abdominal procedures. Its popularity stems from several factors including ease of administration, a shorter learning curve, rapid onset of action, and the establishment of dense surgical anaesthesia [3].

Bupivacaine, an amide-based local anaesthetic, remains the most widely used drug for spinal anaesthesia. Compared to other agents like lignocaine or chloroprocaine, bupivacaine offers higher potency and a longer duration of action, albeit with a slower

onset [4]. Despite its numerous advantages, the primary limitation of using bupivacaine alone for spinal anaesthesia is its relatively short duration of postoperative analgesia.

Pain in the postoperative period continues to be a major concern. A 2014 survey conducted in the United States revealed that 86% of patients experienced postoperative pain, with nearly 75% reporting moderate to severe pain during the immediate recovery phase [5]. In response, both the World Health Organization and the International Association for the Study of Pain have recognized pain relief as a fundamental human right [6]. Poorly controlled postoperative pain is associated with a range of adverse outcomes including increased cardiopulmonary complications, delayed wound healing, heightened risk of surgical site infections, prolonged hospital stay, elevated healthcare costs, and reduced patient satisfaction [7]. Additionally, inadequate pain management during the acute postoperative period is a well-established risk factor for the development of chronic postoperative pain, which can significantly impair the quality of life for years after surgery [8].

To address these challenges, various pharmacological adjuvants have been explored to prolong the duration of analgesia when administered intrathecally along with bupivacaine. These include opioids, benzodiazepines, alpha-2 adrenergic agonists, NMDA antagonists, anticholinesterases, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and vasoconstrictors [9]. Besides extending postoperative analgesia, many of these adjuvants also contribute to prolonging intraoperative anaesthesia, thereby enhancing the overall effectiveness of spinal anaesthesia.

The discovery of opioid receptors in the central nervous system has led to the widespread use of intrathecal opioids as adjuvants to local anaesthetics. When used in combination, intrathecal opioids act synergistically with local anaesthetics to enhance sensory blockade while minimizing the impact on motor function and sympathetic tone. This not only allows for a reduction in the required dose of local anaesthetic but also improves the quality and duration of both intraoperative and postoperative analgesia, all without significantly increasing the risk of adverse effects [10].

Among opioids, morphine—a hydrophilic compound—has been shown to provide prolonged analgesia due to its slower clearance from the cerebrospinal fluid. However, its side effect profile, including pruritus, nausea, vomiting, urinary retention, ileus, sedation, and the risk of delayed respiratory depression due to rostral spread, has limited its widespread use [11]. Consequently, fentanyl, a lipophilic opioid with a more favorable safety profile and quicker onset, has become the most commonly used intrathecal opioid adjuvant.

In recent years, midazolam—a water-soluble benzodiazepine—has emerged as a promising neuraxial adjuvant. Compared to opioids, midazolam is associated with fewer side effects such as allergic reactions, urinary retention, and delayed respiratory depression. Its antinociceptive and muscle relaxant effects are mediated through its action on benzodiazepine receptors, which are part of the GABA-A chloride channel complex. This receptor complex modulates gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Additionally, midazolam is believed to act on delta opioid receptors in the brain and spinal cord [12,13]. Beyond its analgesic properties, midazolam exhibits local anaesthetic-sparing effects, antiemetic benefits, and has shown potential in managing chronic refractory musculoskeletal pain [14].

Despite the theoretical and clinical advantages of both fentanyl and midazolam as intrathecal adjuvants, there is a scarcity of studies directly comparing their efficacy and safety profiles in the Indian population, particularly in the context of lower abdominal surgeries. To address this gap, the present study was designed as a prospective, double-blinded, randomized comparative trial to evaluate and compare the effects of intrathecal midazolam (2 mg) and fentanyl (20 micrograms), when used in conjunction with bupivacaine, on postoperative analgesia in patients undergoing lower abdominal surgical procedures.

Methodology:

Study setting

This prospective, double-blinded, randomized controlled study was conducted at Sri Venkateshwaraa Medical College Hospital & Research Centre, Ariyur, over the period from November 2018 to April 2020. The study population comprised 140 adult patients between the ages of 18 and 60 years, of both sexes, categorized as American Society of Anesthesiologists (ASA) physical status I or II. All patients were scheduled for elective lower abdominal surgeries under spinal anaesthesia and met predetermined eligibility criteria.

Ethical Consideration

The study commenced following approval by the Institutional Human Ethical Committee (Reference

number: SVMCH/IEC/2018-Nov/IEC 21) and registration with the Clinical Trials Registry – India (CTRI/2019/01/017078), ensuring strict compliance with ethical norms throughout the research process. Written informed consent was obtained from all participants before the initiation of study.

Sample Size Determination

Sample size calculation was grounded in the findings of previous clinical trials assessing intrathecal adjuvants, and focused specifically on the duration of grade 4 motor block as the primary outcome variable. Using data from Aasim et al. [15], a target sample size of approximately 67 patients per group was determined. To account for potential dropouts, 70 patients were included in each group, resulting in a total sample size of 140.

Randomization and Group Allocation

Patients were randomly assigned to either of two groups through the sealed envelope technique. Group A received 3 ml (15 mg) of 0.5% hyperbaric bupivacaine combined with 0.4 ml (2 mg) of midazolam administered intrathecally, while Group B received 3 ml (15 mg) of 0.5% hyperbaric bupivacaine with 0.4 ml (20 μg) of fentanyl intrathecally. The allocation and administration of drugs were meticulously maintained to preserve double-blinding: one anaesthesiologist prepared the study medication, while another—unaware of group allocation—performed the block.

Inclusion and Exclusion Criteria

Included in the study were ASA I and II patients, both male and female, aged 18 to 60 years, who were posted for elective lower abdominal surgery. Exclusion criteria consisted of contraindications to spinal anaesthesia, psychiatric illness, and ongoing use of antipsychotic medications.

Preoperative Preparation

All enrolled patients underwent a thorough pre-anaesthetic evaluation. Preoperative medication was standardized with oral administration of pantoprazole (40 mg), metoclopramide (4 mg), and alprazolam (0.25 mg) the night before surgery. Patients were instructed to observe an eight-hour fasting period prior to surgery.

Anaesthesia Technique

On the morning of the surgery, each patient was monitored according to ASA standards, and baseline vital parameters were established. An intravenous preload with Ringer Lactate at 10 ml/kg was administered over 20 minutes. Spinal anaesthesia was performed in the sitting position, using a 25G Quincke spinal needle at either the L3-L4 or L4-L5 interspace, under rigorous aseptic conditions. Upon confirmation of free cerebrospinal fluid (CSF) flow, the study drug was injected slowly over 10–15 seconds. Following administration, patients were positioned supine. The blinding process was reinforced by assigning the preparation of drugs and administration of the block to two separate anaesthesiologists.

Study Parameters

A comprehensive set of demographic and surgical data was collected, including age, gender, height, weight, BMI, ASA status, type, and duration of surgery. Block characteristics were closely observed, including the onset time of sensory and motor block, maximal level of sensory blockade (checked every minute post-injection via pin-prick along the midclavicular line), duration of sensory block (from maximal level to regression by two dermatomes), and duration of motor block (from full block to recovery based on the Modified Bromage Score). The primary outcome—duration of effective analgesia—was defined as the time from anaesthetic injection to patient-reported pain rated at visual analogue scale (VAS) ≥ 3. Pain and sedation were also evaluated using the VAS and Ramsay Sedation Scoring system, respectively, at regular intervals over a 24-hour postoperative period. Intraoperative analgesia quality was rated on a 4-point scale, with supplemental fentanyl administered intravenously in cases of inadequate block. Postoperative analgesic regimens included intramuscular tramadol as first-line therapy, with paracetamol reserved for further analgesic needs according to the standardized protocol.

Monitoring and Management of Side Effects

Vital parameters such as pulse rate, blood pressure, respiratory rate, and oxygen saturation were measured regularly intraoperatively and postoperatively for 24 hours. Adverse events—including hypotension, bradycardia, and oxygen desaturation—were managed following established protocols with intravenous mephenteramine, atropine, or supplemental oxygen, respectively. Patients with inadequate sensory blocks to the T6 level within 30 minutes were excluded and alternative anaesthetic management was instituted. Neurological assessments were performed at 24 hours and again at discharge to rule out persistent neurological impairment.

Statistical Analysis

Data entry was accomplished using Microsoft Excel 2010, and statistical analysis was performed using SPSS version 20.0. Quantitative variables were summarized using means and standard deviations, while qualitative data were expressed as frequencies and percentages. Intergroup comparisons for

continuous variables were conducted using the independent sample t-test, while categorical variables and side effects were analysed using Pearson's Chi-square test. This structured and robust methodological approach provided a thorough comparison of intrathecal midazolam and fentanyl as adjuvants to bupivacaine in spinal anaesthesia for lower abdominal surgeries.

Results:

Table 1: Sociodemographic and Baseline Characteristics

Variable	Group A (n=70)	Group B (n=70)	p-value
Mean Age (years)	45.2 ± 12.7	36.7 ± 8.8	0.060
Gender (M/F)	39/31	40/30	0.865
Mean Height (cm)	165.5 ± 6.8	162.1 ± 9.3	0.162
Mean Weight (kg)	63.9 ± 9.0	65.4 ± 10.8	0.361
Mean BMI (kg/m²)	24.93 ± 3.31	25.43 ± 3.13	0.357
ASA I/II (n)	54/16	52/18	0.473
Mean Duration of Surgery (min)	132.13 ± 24.6	131.19 ± 19.6	0.802

The baseline characteristics of the study population were comparable between Group A and Group B, with no statistically significant differences observed. The mean age was slightly higher in Group A (45.2 ± 12.7 years) compared to Group B (36.7 ± 8.8 years), though this difference did not reach statistical significance (p = 0.060). Gender distribution was nearly identical (39 males and 31 females in Group A vs. 40 males and 30 females in Group B; p = 0.865). Other variables, including mean height (165.5 ± 6.8 cm vs. 162.1 ± 9.3 cm; p = 0.162), weight (63.9 ± 9.0 kg vs. 65.4 ± 10.8 kg; p = 0.361), and BMI (24.93 ± 3.31 kg/m² vs. 25.43 ± 3.13 kg/m²; p = 0.357) also showed no significant differences. ASA physical status distribution was similar between the groups (ASA I/II: 54/16 in Group A vs. 52/18 in Group B; p = 0.473). Furthermore, the mean duration of surgery was comparable between the groups (132.13 ± 24.6 minutes in Group A vs. 131.19 ± 19.6 minutes in Group B; p = 0.802). These findings suggest that the groups were well matched at baseline.

Table 2 : Comparison of Duration of Effective Analgesia, Sensory Block, and Motor Block Between Group A (Midazolam) and Group B (Fentanyl)

Parameter	Group A (Mean ± SD, min)	Group B (Mean ± SD, min)	t-value	p-value
Effective Analgesia	384.43 ± 36.47	335.21 ± 40.78	7.526	0.0001 *
Sensory Block Duration	365.07 ± 35.02	307.97 ± 50.82	7.740	0.0001 *
Motor Block Duration	327.07 ± 25.02	297.97 ± 40.82	5.440	0.021 *

The combined analysis of analgesic efficacy and block duration parameters reveals that Group A (midazolam) consistently outperformed Group B (fentanyl) across all measured outcomes. The mean duration of effective analgesiawas significantly longer in Group A (384.43 ± 36.47 minutes) compared to Group B (335.21 ± 40.78 minutes), with a t-value of 7.526 and a highly significant p-value of 0.0001. Similarly, the duration of sensory block was notably prolonged in Group A (365.07 ± 35.02 minutes) versus Group B (307.97 ± 50.82 minutes), yielding a t-value of 7.740and p-value of 0.0001, again indicating strong statistical significance. The duration of motor block was also greater in Group A (327.07 ± 25.02 minutes) compared to Group B (297.97 ± 40.82 minutes), with a t-value of 5.440 and a significant p-value of 0.021. These results confirm that midazolam, when used as an adjuvant, provides superior and longer-lasting analgesia and block duration than fentanyl in the studied clinical context.

Table 3: Distribution of VAS Scores at Different Time Intervals Among Two Groups

VAS Timing	Group	N	Mean	Std. Deviation	t-value	p-value
VAS (0 hrs)	A	70	0.00	0.00	--	--
	B	70	0.00	0.00		
VAS (1 hr)	A	70	0.00	0.00	--	--
	B	70	0.00	0.00		

VAS (3 hrs)	A	70	0.00	0.00	--	--
	B	70	0.00	0.00		
VAS (5 hrs)	A	70	0.44	0.50	-1.157	0.084
	B	70	1.60	0.49		
VAS (7 hrs)	A	70	0.99	0.12	-71.000	0.0001***
	B	70	2.00	0.00		
VAS (9 hrs)	A	70	0.99	0.12	-1.000	0.319
	B	70	1.00	0.00		
VAS (12 hrs)	A	70	1.97	0.24	-36.000	0.0001***
	B	70	3.00	0.00		
VAS (15 hrs)	A	70	2.97	0.24	69.000	0.0001***
	B	70	1.00	0.00		
VAS (18 hrs)	A	70	1.36	0.74	59.000	0.0001***
	B	70	1.20	0.60		
VAS (24 hrs)	A	70	2.00	0.00	-64.000	0.0001***
	B	70	0.00	0.00		

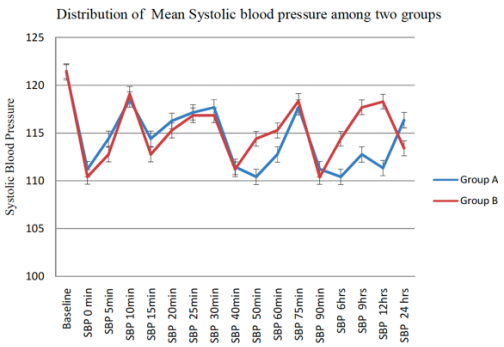
VAS pain scores were significantly lower in Group A at 7, 12, and 24 hours postoperatively, confirming superior analgesic profile for midazolam in those periods.

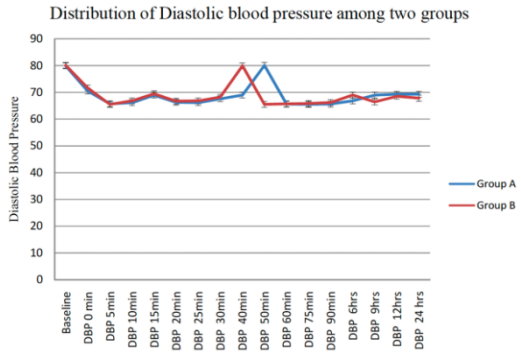
Table 4: Incidence of Adverse Side Effects

Side Effect	Group A (n, %)	Group B (n, %)	p-value
Nausea	8 (11.4%)	9 (12.9%)	0.067
Vomiting	3 (4.3%)	4 (5.7%)	0.035
Pruritus	0 (0%)	12 (17.1%)	0.004**
Respiratory depression	0 (0%)	0 (0%)	--
Urinary retention	0 (0%)	0 (0%)	--

Pruritus was significantly more frequent in the fentanyl group, while other adverse events were rare and comparable between groups.

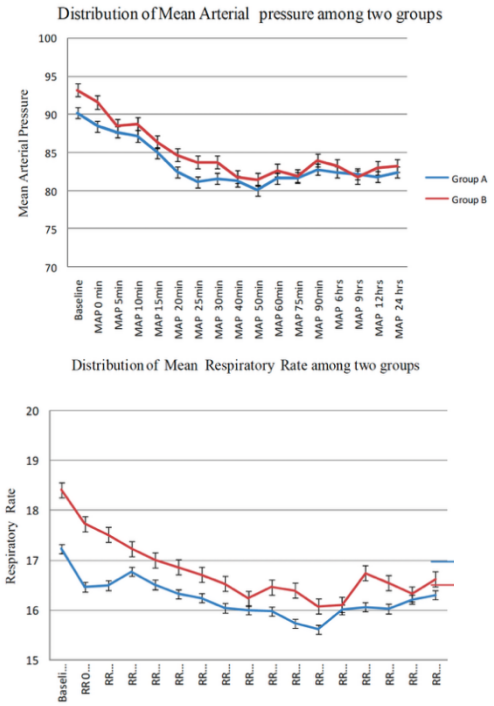
Figure 1 illustrates the differences in rates of systolic blood pressure, diastolic blood pressure, mean arterial pressure, and respiratory rate among the study groups. No significant differences were observed between the two groups at corresponding time intervals up to 24 hours after drug administration. Throughout all parameters, the changes were minimal and did not reach statistical significance, with p-values greater than 0.05. This indicates that both interventions had similar hemodynamic and respiratory effects during the observation period.





1a: Systolic Blood Pressure

1b: Diastolic blood Pressure



1c: Mean Arterial Pressure

1d: Mean Respiratory Rate

Figure 1: Difference of (a) systolic blood pressure, (b) diastolic blood pressure, (c) mean arterial pressure, and (d) respiratory rate among the study groups

DISCUSSION

Subarachnoid block using hyperbaric bupivacaine remains a cornerstone in anesthetic management of lower abdominal and lower limb surgeries due to its reliability, rapid onset, and simplicity. However, the relatively short duration of analgesia necessitates adjuncts to prolong its effects and improve postoperative pain control. Among the various adjuvants explored, opioids like fentanyl and benzodiazepines like midazolam have been the focus of several comparative studies owing to their efficacy and differing side effect profiles.

In the present prospective, randomized, double-blind study, we evaluated the effects of intrathecal midazolam (2 mg) and fentanyl (20 µg) as adjuvants to hyperbaric bupivacaine in 140 patients undergoing elective lower abdominal surgeries. Both adjuvants were effective in enhancing the quality of spinal anesthesia, but several clinically relevant differences were observed.

The addition of midazolam significantly prolonged the duration of sensory and motor block, as well as the duration of effective analgesia, compared to fentanyl. These findings suggest that midazolam, through its action on GABA-A receptors in the spinal cord, may contribute to prolonged segmental inhibition and enhanced antinociception. Our observations are consistent with the findings of Syed Ali Aasim et al. [], who also reported midazolam as being comparable to fentanyl in terms of duration of analgesia, albeit with fewer side effects. On the other hand, studies by Anupama Gupta et al. [53] and Halalu Shankaregowda Suraj et al. [54] reported a more pronounced and prolonged analgesic effect with fentanyl over midazolam, which contrasts with our results. These discrepancies may be attributable to differences in dosage, patient population, and surgical settings.

The onset of sensory and motor block was found to be comparable between both groups. Several previous studies, including those by Syed Ali Aasim et al., and Anupama Gupta et al., support this observation, reporting no significant difference in onset times between midazolam and fentanyl when used intrathecally [15,16]. While Halalu Shankaregowda Suraj et al. [17] noted a faster onset in the fentanyl group, our findings did not replicate this, potentially due to variations in injection technique, drug concentrations, or interindividual pharmacodynamic differences.

Interestingly, the requirement for rescue analgesia was significantly lower in the midazolam group, which underscores its prolonged efficacy in the postoperative period. This contrasts with the findings by Halalu Shankaregowda Suraj et al. [17], where fentanyl was reported to delay the need for rescue analgesia longer than midazolam. Differences in analgesic protocols or thresholds for administering rescue medication could explain this divergence.

From a safety perspective, our study demonstrated a better side effect profile with midazolam. Pruritus and nausea were significantly more frequent in the fentanyl group, aligning with earlier studies by Syed Ali Aasim et al. [15] and Anupama Gupta et al. [16]. Notably, none of the patients in the midazolam group experienced pruritus, which further advocates its use as a favorable alternative to opioids in select patient populations. Although no serious adverse events like respiratory depression or sedation were noted in either group, the incidence of opioid-related side effects, though mild, reaffirms the need for cautious use, especially in settings where postoperative monitoring may be limited.

Hemodynamic parameters, including pulse rate, systolic and diastolic blood pressure, and oxygen saturation, remained stable across both groups throughout the observation period. These findings, which are consistent with prior reports [18-20], suggest

that both adjuvants are hemodynamically safe when used in appropriate doses along with bupivacaine for spinal anesthesia.

The findings of this study have important implications for clinical practice. Midazolam, due to its prolonged analgesic effect and favorable side effect profile, may serve as a valuable alternative to opioids, particularly in patients where opioid-related side effects are a concern. Moreover, its anxiolytic properties can also benefit patients undergoing regional anesthesia by reducing perioperative anxiety.

However, the study is not without limitations. First, the follow-up period was limited to the immediate 24-hour postoperative phase; long-term neurological safety of intrathecal midazolam, although well-supported by prior literature, was not evaluated in our cohort. Lastly, while the sample size was adequate for primary outcome measures, further multicentric studies with larger populations and longer follow-up are necessary to confirm these findings.

Midazolam appears to be a viable alternative to fentanyl as an intrathecal adjuvant to bupivacaine, particularly in resource-constrained settings or where opioid side effects need to be minimized. Its use could help reduce the need for postoperative analgesics and improve patient comfort. However, caution is advised in extrapolating these findings universally, and clinicians should consider patient-specific factors when choosing intrathecal adjuvants.

Conclusion:

In this study comparing intrathecal midazolam and fentanyl as adjuvants to hyperbaric bupivacaine for spinal anesthesia in elective lower abdominal surgeries, midazolam demonstrated a longer duration of sensory and motor block, prolonged postoperative analgesia, and a reduced requirement for rescue analgesics compared to fentanyl. Additionally, midazolam was associated with fewer side effects, particularly avoiding opioid-related complications such as pruritus and nausea. Both agents maintained stable hemodynamic and respiratory profiles throughout the perioperative period. These findings suggest that intrathecal midazolam is a safe and effective alternative to fentanyl for enhancing the quality and duration of spinal anesthesia, especially in settings where minimizing opioid-related side effects is desirable.

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