International Journal of Health Science & Biomedicine (IJHSB)
e-ISSN: 3139-3691

RESEARCH ARTICLE OPEN ACCESS

Analgesic Efficacy of Intrathecal Hyperbaric Bupivacaine Alone versus Pre-mixed and Sequential Fentanyl-Bupivacaine for Caesarean Section: A Randomized Controlled Trial

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Citation: Destaw B, Kebede D, Garola G, Gashaw A, Adamu Y (2026). Analgesic Efficacy of Intrathecal Hyperbaric Bupivacaine Alone versus Pre-mixed and Sequential Fentanyl-Bupivacaine for Caesarean Section: A Randomized Controlled Trial. Int J Health Sci Biomed. 3(5): 1-8.

Received Date: 2026-10-05, **Accepted Date:** 2026-10-10, **Published Date:** 2026-10-31

Keywords: Analgesia; Hyperbaric, Fentanyl; VAS score; Ethiopia

Abstract

Introduction: The optimal method for administering intrathecal fentanyl with hyperbaric bupivacaine for caesarean sections remains unclear. This study evaluated the analgesic effectiveness of sequential versus premixed intrathecal fentanyl, as well as bupivacaine alone, in women undergoing elective caesarean sections.

Method: A double-blind randomized controlled trial was conducted with 192 ASA II parturient women undergoing elective caesarean sections under spinal anesthesia at Dilla University Teaching Hospital in Ethiopia. The study ran from May 2021 to October 2022. Participants were randomly assigned to three groups: Group B received 12.5 mg of hyperbaric bupivacaine alone; Group M received 10 mg of hyperbaric bupivacaine mixed with 25 µg of fentanyl; and Group S received 10 mg of hyperbaric bupivacaine followed by 25 µg of fentanyl. The primary outcome was postoperative pain measured by the visual analog scale (VAS). Secondary outcomes included time to the first request for analgesics, block characteristics, analgesic use, adverse events, and neonatal outcomes.

Results: VAS pain scores were significantly lower in Groups S and M than in Group B at several postoperative time points ($p < 0.05$). However, no consistent statistically significant difference was observed between Groups S and M. The mean time to the first analgesic request was significantly longer in Group S (248 ± 42.6 min) and Group M (229 ± 35.1 min) than in Group B (178 ± 34.2 min) ($p < 0.001$). The duration of motor block was longer in Group S ($p = 0.006$). Hypotension occurred more often in Group M than in Group S ($p = 0.040$). Neonatal APGAR scores were similar across the groups.

Conclusion: Intrathecal fentanyl improved postoperative analgesia compared with bupivacaine alone. However, differences between sequential and pre-mixed administration techniques were modest and of uncertain clinical significance. Further multicentre studies are recommended.

Trial Registration: Pan African Clinical Trial Registry: PACTR202205853184065 (retrospectively registered)

Introduction

Spinal anesthesia is the optimal anesthetic technique for caesarean section due to its rapid onset, high success rate, reduced maternal airway complications, and minimal neonatal drug exposure. However, limited postoperative analgesia remains one of its major drawbacks. Effective postoperative pain control is essential for early mobilization, maternal satisfaction, breastfeeding, and prevention of postoperative complications [1].

The Ethiopian demographic health survey found the Addis Ababa CD rate was 22%, which is higher than the WHO recommendations, as treatments for pregnancy are [2]. Private health facilities performed more CS than public health facilities, 41.1% and 11.7%, respectively, and it was high amongst women of higher socioeconomic standing [2].

Intrathecal opioids, particularly fentanyl, are commonly added to hyperbaric bupivacaine to improve the quality and duration of analgesia. Fentanyl is relatively hypobaric compared to cerebrospinal fluid, whereas hyperbaric bupivacaine has a higher density. When mixed, the resulting solution remains predominantly hyperbaric, which may explain the minimal changes in intrathecal spread. In contrast, sequential administration may influence drug distribution due to differences in density and cerebrospinal fluid dynamics [3].

Previous studies comparing sequential and pre-mixed intrathecal administration techniques have reported inconsistent findings regarding analgesic efficacy and block characteristics between the techniques [4,5]

Therefore, this study aimed to compare the analgesic efficacy, block characteristics, analgesic consumption, and adverse effects of

sequential versus pre-mixed intrathecal fentanyl administration with hyperbaric bupivacaine among parturient undergoing elective caesarean section.

We hypothesized that sequential intrathecal administration of fentanyl with hyperbaric bupivacaine would provide superior postoperative analgesia compared with pre-mixed administration and bupivacaine alone.

Methods

Study Design, Rrea and Period

A double-blind randomized controlled trial was conducted at Dilla University Teaching Hospital, Ethiopia, from May 1, 2021 to October 30, 2022.

Sample Size Determination

The sample size was calculated using a two-sided alpha of 0.05 and a statistical power of 80% with 95% confidence interval based on expected differences in postoperative pain scores among the study groups assessed by the Visual Analog Scale (VAS), using proportions adapted from the study by Chekole AT et al., [6], which compared sequential versus pre-mixed intrathecal fentanyl with hyperbaric bupivacaine for elective caesarean section. A total sample size of 192 participants (64 per group) was included.

$$= \frac{P_1(1-P_1)+P_2(1-P_2)}{(P_2-P_1)^2} \times f(\alpha, \beta)$$

Accordingly, the minimum sample size was approximately 55 participants per group. After adding a 10% contingency for possible attrition and incomplete data, the final sample size became 64 participants per group. Therefore, a total of 192 parturient (64×3) were enrolled in the study.

Sampling Procedure and Technique

Randomization and Allocation Concealment

Participants were recruited consecutively and randomly assigned into one of the three study groups using a computer-generated randomization sequence prepared by an independent anesthetist not involved in patient care. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes opened immediately before spinal anesthesia administration.

Blinding

Participants and postoperative outcome assessors were blinded to group allocation. The anesthetist administering spinal anesthesia was aware of the intervention because of the nature of the procedures but was not involved in postoperative assessment or data analysis. Data analysis was performed by an investigator blinded to group allocation.

Study Interventions

- Group B: 12.5 mg hyperbaric bupivacaine alone
- Group M: 10 mg hyperbaric bupivacaine mixed with 25 μg fentanyl
- Group S: 10 mg hyperbaric bupivacaine followed sequentially by 25 μg fentanyl

The total intrathecal injectate volume was standardized as much as possible among groups

The intrathecal dosing strategy in this study was based on evidence supporting the synergistic effect of fentanyl with low-dose hyperbaric bupivacaine in spinal anesthesia for caesarean section. Group B received 12.5 mg bupivacaine alone, while Groups M and S received 10 mg bupivacaine with fentanyl to reduce local anesthetic dose while maintaining adequate anesthesia and hemodynamic stability. Previous randomized controlled trials have shown that adding fentanyl allows effective reduction of bupivacaine dose without compromising block quality or analgesia (Ben-David et al., 2000; Desai et al., 2010). Dose-controlled studies further support using a fixed bupivacaine dose with varying fentanyl to isolate opioid effects on analgesia and block characteristics (Desai et al., 2010), confirming that observed differences are mainly attributable to fentanyl rather than local anesthetic dose variation (Alkaissi et al., 2026) [7-9].

Outcome Measures

Primary Outcome

Postoperative pain intensity assessed using the visual analogue scale (VAS).

Secondary Outcomes

- Time to first analgesic request
- Sensory block characteristics
- Duration of motor block
- Postoperative analgesic consumption
- Incidence of adverse events
- Neonatal APGAR scores at 1 and 5 minutes

Inclusion Criteria

- ASA physical status II parturient
- Age between 18 and 40 years
- Scheduled for elective cesarean section under spinal anesthesia

Exclusion Criteria

- Contraindications to spinal anesthesia
- Known hypersensitivity to study drugs
- Pre-existing neurological or spinal disorders
- Pregnancy complications requiring general anesthesia
- Refusal to participate

Operational Definitions

VAS: Pain intensity was assessed using the Visual Analogue Scale (VAS), a 10-cm scale ranging from 0 (no pain) to 10 (worst imaginable pain). Participants were asked to indicate their perceived pain intensity by marking a point on the scale, and the score was recorded accordingly [10].

Total analgesic consumption: the total amount of analgesic the patient is given after the spinal anesthesia within 24 hours.
Regression of motor block: regression of modified Bromage score of 3 to score of 0 [11].
Onset of sensory block: defined as the loss of sensation at the T10 dermatome [11].
Time to first analgesic request: the time in hours (minutes) measured from the end of the spinal anesthesia procedure to the time when the patient requests analgesics

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Pre-mixed: mixing with one syringe before administration
ASA status: a surgical risk stratification validated by the American Society of Anesthesiologists.
Shivering grade: which is a more objectively expressed and statistically quantifiable shivering scoring way, was described and validated by Tsai and Chu [13].

Clinical Outcome Measurement Variable

Preoperatively

All patients fasted for 8 hours for solid food and 2 hours for clear fluids. They were premeditated with ranitidine 150mg the night before the operation. Information regarding the study and its benefits, risks, and objectives was provided to eligible parturient the night before the operation. An 18-gauge IV cannula was inserted after midnight to administer maintenance fluids to the patients. Preoperative patient information was obtained from the charts and through direct assessment.

The study drugs were presented as coded syringes by an anesthetist who was not involved in patient management. Upon arrival in the operating theatre, patients scheduled for elective caesarean section were randomly allocated into one of three groups using shuffled opaque sealed envelopes containing codes. Each group consisted of 64 parturient. Group M received spinal anesthesia with 10 mg hyperbaric bupivacaine (0.5%) premixed with 25 µg fentanyl in the same syringe. Group S received the same medications sequentially but without premixing, using two different syringes: first 10 mg hyperbaric bupivacaine followed by 25 µg fentanyl without barbotage. Group B served as the control group and received 12.5 mg of hyperbaric bupivacaine alone.

All medications were prepared before the insertion of the spinal needle. Demographic data, including age, height, and weight, were documented from the charts. In the operating room, the patient was positioned supine, and fluid loading with 10-15 ml/kg of normal saline was administered. Standard monitoring, including electrocardiogram, heart rate (HR), non-invasive blood pressure, thermometer, and pulse oximetry, was applied. Baseline VAS scores and hemodynamic variables (Blood pressure, HR, and oxygen saturation [SPO2]) were recorded before spinal anesthesia.

The patient was then positioned in a sitting position, and skin infiltration was performed at the entry point of L3/L4 or L4/L5 with 2% plain lidocaine (2ml) using a strict aseptic technique with iodine and alcohol. Spinal anesthesia was administered by the anesthetist using 22–25-gauge spinal needles at either L3-L4 or L4-L5, based on the group allocation. The respective drugs were administered accordingly. For the sequential group, the timing between the first and second syringes was minimized to prevent cerebrospinal fluid (CSF) leakage. The sensory and motor blocks were assessed using pinprick and the Bromage scale, respectively, with the desired sensory block at T6-T4 and Bromage scale 3.

IV fluid co-loading with 15 ml/kg lactated Ringer's solution was administered as a fast drip during and after spinal anesthesia through an 18-gauge IV cannula. Motor blockade of the lower limbs was tested and scored using the modified Bromage scale, assessing the ability to raise an extended leg, flex the knee, or flex the ankle. Motor block assessments were conducted every 5 minutes for 30 minutes. The time of onset and duration of motor blockade, as well as the time elapsed from the start of motor block until complete recovery of muscle strength, were determined.

Segmental sensory levels of anesthesia were assessed through the patient's response to pinprick, and the onset of sensory blockade was measured by the time from the injection of study drugs to the complete abolition of pinprick sensation.

If the block failed to reach T6, 15 minutes after spinal injection, general anesthesia was induced using a rapid sequence induction technique [14].

Intraoperatively

Patients' peripheral oxygen saturation, heart rate, blood pressure, and electrical activity of the heart were measured every 5-10 minutes and recorded based on the data collection tool throughout the surgical procedure. Pulse rate, systolic blood pressure, diastolic blood pressure, and SpO2 were recorded at different time intervals: 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, and 1 hour. Side effects such as hypotension, bradycardia, shivering, nausea, and vomiting were documented. If a patient's heart rate dropped below 50 beats per minute, IV atropine 0.5 mg was administered. Hypotension was treated with 6 mg of IV ephedrine and crystalloids. In cases of grade 1 or higher nausea and vomiting, metoclopramide 10 mg was administered intravenously. Shivering of grade 2 or higher was managed by administering oxygen and 25 mg of pethidine. Oxygen at a rate of 4 L/minute was administered via a face mask throughout the intraoperative period, and patients were covered with drapes. If pruritus occurred, its severity was assessed, and severe pruritus (unbearable, requiring treatment) was managed with 4 mg of ondansetron. Any events during the intraoperative period were managed according to the protocol.

After delivery, 20 IU of oxytocin was added to 1000 ml of normal saline and infused at a rate of 0.02 IU/min. The neonate was dried and received standard care from midwives. APGAR scores were recorded at one and five minutes, and if neonatal resuscitation was needed, it was conducted according to the protocol outlined in the annex.

Postoperatively

As part of multimodal analgesia, each patient was given 1 mg/kg of diclofenac on a TID (three times a day) basis, starting immediately upon arrival in the post-anesthetic care unit (PACU).

Side effects such as hypotension, bradycardia, pruritus, shivering, nausea, and vomiting were recorded. If the Visual Analogue Scale (VAS) score was above 3 points, patients received 1 mg/kg of IM diclofenac sodium along with 20 mg/kg of PO paracetamol. If this treatment was inadequate within 30 minutes, 1-2 mg/kg of tramadol was added. If the pain relief was still ineffective within another 30 minutes, an additional 0.1 mg/kg of IM morphine was administered. Any events during the post-operative period were managed according to the protocol.

The severity of pain and hemodynamic parameters were recorded every 30 minutes for the first 4 hours postoperatively, then every 1 hour until the 12th postoperative hour, and finally every 6 hours from the 12th to the 24th postoperative hour, resulting in a total of 18 postoperative observations.

Rescue analgesia was provided to patients based on the WHO analgesic ladder. The time from the onset of the sensory block to the first request for analgesics was documented. Any complications associated with spinal anesthesia were managed accordingly.

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Data Collection Method

Data was collected from the clinical charts of mothers who underwent a caesarean section. The necessary information, including consent details, study descriptions, benefits, potential harms, and study objectives, was prepared in English and translated into Amharic. The data collection tool, filled by the data collectors, was also prepared in English. The questionnaire included sociodemographic data (age, sex, ASA status, weight, BMI, and patient diagnosis), which could be retrieved from the patient's charts and anesthesia preoperative record charts. It also contained baseline, intraoperative, and postoperative hemodynamic and analgesia-related parameters. Eight trained BSc anesthetists, who were blinded to the study, were involved in the data collection process. Additionally, two MSc anesthetists and one senior midwife supervised each data collection process.

Data Quality Control Management

A pre-test of the data collection tool (questionnaire) was conducted on 10% of the patients to ensure data quality. The accuracy and clarity of the data collection tool were assessed, and necessary corrections were made to the questionnaire for the main study. To maintain data quality, training was provided to data collectors and supervisors on how to use the assessment tool. Patients were also informed before the operation on how to report any intraoperative complaints they may have. During data collection, regular supervision and follow-up were carried out. Each data collection tool had a checklist for checking data accuracy. Supervisors reviewed each questionnaire daily, and the principal investigator conducted further cross-checks to ensure the completeness and consistency of the data.

Data Analysis and Processing

Data were analysed using SPSS version 25. Continuous variables were assessed for normality and analysed using one-way ANOVA or Kruskal–Walli's test as appropriate. Categorical variables were analysed using Chi-square test or Fisher's exact test. Kaplan–Meier survival analysis was used to compare time to first analgesic request among groups. Repeated postoperative measurements were analysed at individual time points; however, no formal repeated-measures statistical model was applied. A p-value < 0.05 was considered statistically significant.

Result

Demographic and Perioperative Characteristics of the Study Participants.

A total of 192 samples (64 pregnant mothers in each group) were involved in the analysis of the study. There was no statistically significant difference among the groups in demographic data and intraoperative characteristics [Table 1].

Comparison of Postoperative Pain Severity by VAS Scale

The results were similar at 30 minutes, 1 hour, 2 hours, 6 hours, 8 hours, 12 hours, and 24 hours. However, the median pain scores were significantly lower in the M-group and S-group compared to the B-group at 3 hours, 4 hours, and 16 hours, with p-values of 0.001, 0.002, and 0.013, respectively (p < 0.05) [Table 2].

Variables	B-group	M-group	S-group	P-Value
Age(yr.)	26.8±3.55	29.0±5.27	27.0±5.12	0.522
Weight(kg)	71.7±15.5	74.4±16.5	74.6±12.1	0.888
Height(cm)	163.4±6.83	166.2±3.79	166.0±6.44	0.499
BMI (Kg/M2)	26.71±4.21	26.05±3.65	27.11±4.87	0.851
Blood Loss(ml)	387.0±63.4	461.0±129.9	422.0±115.9	0.373
Intraoperative Fluid(ml)	2250±716.8	1950±550.2	1800±258.2	0.187
Baseline MAP	82.7±6.20	87.3±8.71	85.6±16.2	0.657
Baseline HR	87.8±11.61	84.9±8.37	86.4±16.99	0.881

NB: Result presented as Mean±SD, S-sequential group, M-pre-mixed group, cm-centimeter, kg-kilogram, m2-meter square, Min-Minute, BMI-Body mass index, ml-milli liter, SD-standard deviation, P-value <0.05 was considered as significant

Table 1: Demographic data and intraoperative characteristics of the parturient who underwent C/S.

Time	B-group	M-group	S-group	P-value
VAS at 30 min	1(1-1)	1(1-1)	1(1-1)	1
VAS at 1hr	1(1-1)	1(1-1)	1(1-1)	1
VAS at 2hr	1(1-2)	1(1-2)	1(1-1)	0.186

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VAS at 3hr	2(1-3)	1(1-3)	1(1-1)	0
VAS at 4hr	2(1-5)	1(1-3)	1(1-2)	0.002
VAS at 6hr	1(1-2)	1(1-2)	1(1-3)	0.24
VAS at 8 hr.	1(1-1)	1(1-2)	1(1-2)	0.585
VAS at 12 hr.	1(1-2)	1(1-1)	1(1-1)	0.585
VAS at 16 hr.	1.5(1-3)	1(1-2)	1(1-3)	0.013
VAS at 24 hr.	1(1-3)	1(1-2)	1(1-2)	1

Abbreviation: hr. = hour, VAS-visual analogue scale

Table 2: Comparison of Postoperative pain VAS score among the groups (B, M, S) in patients who underwent elective C/S

Comparison of first rescue analgesic request time and post-operative consumption of analgesia between groups

The mean time to the first request for analgesia was longer in the S group compared to both the M group and the bupivacaine alone group. Additionally, the time in the M group was extended compared to the bupivacaine alone group. Furthermore, the median total consumption of tramadol was lower in the S group,while the total consumption of pethidine did not show significant differences between the groups [Table 3].

Characteristics of a Block

There was no significant difference in the maximum level of sensory block among the three groups ($p > 0.05$), but regarding the duration of motor block, there was a statistically significant difference among the groups [Table 4].

Variables	**B-group**	**M-group**	**S-group**	**P-value**
First Rescue Analgesic request time	178.00±34.2 5	229.00±35.10	248.00±42. 63	0.001
Total Analgesic Consumption				
Tramadol (IM)	75(75)	50(50-72.5)	50(50)	0.059
Pethidine (IV)	0(0)	0(0)	0 (0)	0.102

NB: Result presented as*=M±SD in minutes,**=median (IQR), IM-Intramuscular-Intravenous<0.05 was considered as statistically significant

Table 3: The first rescue analgesic request time and total analgesia consumption among groups (B, M, and S) were shown in patients who underwent elective C/S under spinal anesthesia

Variables	B-group	M-group	S-group	P-value
Time taken for onset of sensory block				
Time taken for onset of motor block	5.1±1.7	5.0±1.9	4.4±2.9	0.757
Maximum level of sensory Block	T6	T6	T6	1

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Sensory regression	124.8±45.7	187.2±42.1	189.0±74.6	0.025
Duration of motor block	187.0±40.8	250.0±49.9	274.0±74.7	0.006

NB: Values, *: median (IQR) in minute,**: mean ± SD in minute, where, IQR =interquartile range and SD = standard deviation, T = Thoracic dermatome, p-value < 0.05 was considered as statistically significant

Table 4: Comparison of block character between the two groups who undergone elective Cesarean Section under spinal anesthesia

Comparisons of incidence of intraoperative complication among the groups

The incidence of hypotension was significantly higher in the pre-mixed group compared to the sequential group (p=0.040), while the incidence of bradycardia, nausea, vomiting, pruritus, and shivering was comparable among groups. No cases of respiratory depression were observed.

No consistent statistically significant difference was observed between the sequential and pre-mixed groups for most postoperative outcomes.

Neonatal APGAR scores at 1 and 5 minutes were comparable across all groups, with no statistically significant differences observed.

Discussion

This study evaluated the analgesic effectiveness of three different methods for administering bupivacaine during elective caesarean sections: bupivacaine alone (B-group), bupivacaine combined with fentanyl (M-group), and a sequential approach of bupivacaine followed by fentanyl (S-group).

Although statistically significant differences were observed in some outcomes, particularly time to first analgesic request and duration of motor block, the clinical relevance of these differences appears modest, especially between the sequential and pre-mixed techniques.

The findings of the present study are consistent with previous studies reporting limited clinical advantage of sequential intrathecal fentanyl administration compared with pre-mixed administration. The minimal difference observed may be explained by the fact that the final fentanyl-bupivacaine mixture remains predominantly hyperbaric, resulting in only minor alterations in intrathecal spread [15]

Analgesic Efficacy

The findings of this study indicate that both the M-group and S-group showed significantly better pain relief compared to the B-group.

First Analgesia Request time

The average time until the first request for analgesia was considerably longer in the S-group (248.00 ± 42.63 minutes) and M-group (229.00 ± 35.10 minutes) than in the B-group (178.00 ± 34.25 minutes, P = 0.001). This improvement in analgesic duration aligns with earlier research, such as that by Uppal et al., which found an increase of 91 minutes in the time to the first request for postoperative analgesia when fentanyl was added to bupivacaine [16]. This study result is also supported by another Systematic review and analysis conducted by Abate S. and his colleagues stated that there was a prolonged sensory regression in the fentanyl-bupivacaine group when compared to the Bupivacaine alone group [17].

The sequential administration method (S-group) seems to prolong this duration further. Desai et al. Discovered that low-dose bupivacaine combined with fentanyl led to a longer period of effective pain relief, highlighting the potential of sequential techniques to enhance pain management in the postoperative phase [18].

This is also in line with the study conducted by Sonali J. and his Colleagues, which showed that there was a statistically significant difference among the groups in which the S group had a prolonged first analgesia request time [19].

Postoperative Pain Scores

Analysis of postoperative VAS pain scores showed significant differences among the groups. Both the M-group and S-group reported lower pain scores compared to the B-group at critical time intervals: at 3 hours (B: 2 [1-3] vs. M: 1 [1-3], S: 1 [1-1], P = 0.001) and at 4 hours (B: 2 [1-5] vs. M: 1 [1-3], S: 1 [1-2], P = 0.002). This suggests that adding fentanyl, whether mixed or given sequentially, significantly enhances pain relief. These results are consistent with Desai et al.'s findings, which indicated that patients receiving a combination of bupivacaine and fentanyl experienced better pain management than those given bupivacaine alone [3-7]

Duration of Motor Block

Although there were no significant differences in the maximum sensory block level among the three groups, the duration of motor block was significantly longer in the S-group (274.0 ± 74.7 minutes) compared to the M-group (250.0 ± 49.9 minutes) and B-group (187.0 ± 40.8 minutes, P = 0.006). This increased duration of motor block in the S-group may offer additional advantages in certain surgical situations that require prolonged anesthesia. This finding aligns with earlier research, such as that by Sonali Joshi, which suggested that sequential administration techniques could enhance motor block duration while maintaining safety [19].

Likewise, Hussien RM and Rabie observed that sequential intrathecal injection techniques influenced block characteristics, particularly by prolonging motor block duration and improving the quality of spinal anesthesia without increasing major adverse effects. Their randomized controlled trial further indicated that sequential administration may alter intrathecal drug distribution because of differences in the baricity and density of fentanyl and hyperbaric bupivacaine, potentially contributing to enhanced anesthetic effects and longer motor blockade [15].

Side Effects

The occurrence of side effects, especially pruritus, was observed in the M-group at a rate of 14%. In comparison, no patients in the B group experienced pruritus. Although the S-group did not report any cases of pruritus, the presence of this side effect is an important factor to consider when selecting an analgesic technique. The heightened risk of pruritus linked to fentanyl use is supported by Uppal et al, emphasizing the necessity for

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careful patient monitoring and informed consent regarding potential side effects when utilizing fentanyl [20].

Implications for Clinical Practice

The results of this study indicate that the sequential administration of bupivacaine and fentanyl may be an effective method for managing pain in elective caesarean sections. The notable enhancements in analgesic duration and pain scores, along with a satisfactory safety profile, highlight the advantages of this technique. Clinicians might consider implementing sequential administration as a standard practice to improve postoperative pain relief and increase patient satisfaction.

Limitation and Future research

A key limitation of this study is the difference in bupivacaine dose between the control group and fentanyl groups, which may confound interpretation of the observed effects. Additionally, repeated measurements were analyzed at individual time points without application of a formal repeated-measures statistical model, which may increase the risk of type I error.
Despite these limitations, the study provides clinically relevant data regarding intrathecal fentanyl administration techniques in a resource-limited setting.

Conclusion and Recommendation

Intrathecal fentanyl significantly improved postoperative analgesia compared with hyperbaric bupivacaine alone in cesarean section. However, the differences between sequential and pre-mixed administration techniques were modest and of uncertain clinical significance. Further multicenter randomized studies are required to confirm these findings.

List of Abbreviations

ADRs: Adverse drug reactions, **ASA**- American Society of Anesthesiology, **BMI**- Body mass index, BSc- Bachelor of Science, **CD:** Caesarean delivery, **CM:** centimetre, **CNS:** Central nervous system, **CS**- Caesarean section, **CSF**- Cerebrospinal fluid, DBP: Diastolic blood pressure, **DC**- data collector, **ETB**- Ethiopian birr, HB- Hyperbaric Bupivacaine, **HR:** Heart rate, IM: Intramuscular, **IQR:** Intra quartile range, **IV:** Intravascular, **L3:** The 3rd lumbar vertebrae, **L4:** The 4th lumbar vertebrae, **L5:** The fifth lumbar vertebra, M- pre-mixed group, **MAP:** Mean arterial pressure, **MG:** Milligram, ML: Milli Liter, MSc Master of science, **NRS**- numerical rating scale, **PACU:** Post-anesthesia care unit, PI- principal investigator, **PO:** Per oral, **S**- Sequential group, SA- spinal anesthesia, **SBP:** Systolic blood pressure, **SD:** Standard deviation, **SPSS**- Statistical Package for Social Sciences, T4: The 4th thoracic vertebrae, **T6:** The 6th thoracic vertebrae ,**TID:** Three times per day, **VAS**- visual analogue score ,WHO- World health organization.

Declarations

Ethical approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of Dilla University, College of Medicine and Health

Sciences, Ethiopia (Reference No: DUCHM/IRB/047/2021). Written informed consent was obtained from all participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Conceptualization: Belete Destaw
Methodology: All authors
Data Collection: All authors
Data Analysis: Belete Destaw
Writing Original Draft: Belete Destaw
Writing Review & Editing: All authors

Acknowledgments

First and foremost, we would like to express our gratitude to all of the participants in the study as well as the data collectors.

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Citation: Destaw B, Kebede D, Garola G, Gashaw A, Adamu Y (2026). Analgesic Efficacy of Intrathecal Hyperbaric Bupivacaine Alone versus Pre-mixed and Sequential Fentanyl-Bupivacaine for Caesarean Section: A Randomized Controlled Trial. Int J Health Sci Biomed. 3(5): 1-8.