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# Outcomes of spinal anesthesia for elective cesarean section using bupivacaine combined with different doses of intrathecal fentanyl: A randomized double-blind clinical trial

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## Abstract

**Background:** Currently, there is no consensus on the optimal dose of fentanyl that should be combined with bupivacaine in spinal anesthesia for cesarean section deliveries. **Objective:** To determine the optimal dose of intrathecal fentanyl to be combined with bupivacaine that is needed to obtain an optimal mix of sensory and motor block, analgesia, and acceptable incidence of adverse effects in spinal anesthesia for cesarean section deliveries. **Methods:** A prospective, randomized, double-blind clinical trial that was conducted in adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Women who opted for elective cesarean section deliveries were randomized into 4 groups. Groups 1-3 received 7.5 mg of 0.5% hyperbaric bupivacaine with 10, 15, and 25 μg of fentanyl, respectively. Group 4 received 10 mg of 0.5% hyperbaric bupivacaine without fentanyl. Sensory and motor block, analgesia, hemodynamic stability, the incidence of adverse effects, and neonatal health outcomes were assessed. **Results:** A total of 160 women completed the study (40 women in each group). The women who received 25 μg of fentanyl with 7.5 mg of 0.5% hyperbaric bupivacaine had significantly shorter (p-value $< 0.0001$) sensory block latency, longer duration of sensory block, longer duration of analgesia, less need for rescue analgesia, expressed higher satisfaction with analgesia, experienced less hemodynamic instabilities, and experienced fewer episodes of bradycardia and vomiting compared to those who received bupivacaine alone or in combination with lower doses of fentanyl. On the other hand, more episodes of pruritus were reported when bupivacaine was combined with fentanyl compared to bupivacaine alone (p-value $< 0.01$). **Conclusions:** The combination of 25 μg intrathecal fentanyl with 7.5 mg of 0.5% hyperbaric bupivacaine in spinal anesthesia for cesarean section was associated with a favorable balance of sensory blockade, motor blockade, analgesia, and adverse effects. However, the increased incidence of pruritus should be considered.

## Keywords

bupivacaine, cesarean section, spinal anesthesia, intrathecal opioids, fentanyl, randomized controlled trial

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## 1. Introduction

Elective cesarean section is one of the most commonly performed surgical operations in obstetrics practice. Over the past few decades, women from different regions of the world have increasingly elected to have planned cesarean section deliveries without emergency or medical indications.[1–4] Previous studies have shown that in some regions, like the US, cesarean section delivery rates were as high as 65%.[5] It has been argued that elective cesarean section deliveries were shown to be associated with less risk for pelvic organ prolapse, urinary, and fecal incontinence compared to vaginal deliveries.[6] Additionally, cesarean section deliveries were shown to be associated with less risk for fetal heart abnormalities, chorioamnionitis, breech presentation, and cord prolapse compared to vaginal deliveries.[7] The other perceived benefits of cesarean section deliveries include avoiding labor pain and anxiety, the convenience of a scheduled delivery, and fewer concerns about the health of the delivered baby.[7,8]

Cesarean sections can be performed under general, spinal, epidural, and combined spinal-epidural anesthesia. In today's obstetrics practice, cesarean sections are increasingly performed under spinal anesthesia.[9,10] Spinal anesthesia is often safe, economical, and ensures achieving rapid anesthesia and adequate analgesia.[9,11] On the other hand, spinal anesthesia can be associated with hypotension.[12] It is worth noting that applying spinal anesthesia can be challenging to the anesthesiologists as well as the providers of obstetrics care services. In obstetrics practice, hyperbaric bupivacaine is one of the most widely used local anesthetics to induce spinal anesthesia in elective cesarean section deliveries.[13] Spinal anesthesia with bupivacaine is easy to perform, ensures quick installation of anesthesia, has a low cost, often provides adequate analgesia, and adequate muscle relaxation.[14]

To ensure obtaining adequate levels of sensory block and analgesia, 12-15 mg doses of hyperbaric bupivacaine are needed. These high doses were shown to be associated with an increased risk for hypotension and fetal distress.[15] Reducing the dose of the local anesthetic has been suggested as a strategy to reduce the risk of hemodynamic instabilities. However, reducing the local anesthetic dose may compromise adequate analgesia. Therefore, complementary analgesics would be needed to avoid visceral pain and pain due to the surgery. Previous studies have shown that fentanyl can be combined with lower doses of bupivacaine to ensure achieving adequate levels of sensory block and analgesia.[14] Intrathecal fentanyl doses that ranged from 2.5-50 μg were combined with bupivacaine to ensure an optimal mix of sensory block, analgesia, and acceptable incidence of adverse effects.[14,16–18]

Fentanyl is a highly lipophilic opioid analgesic that has a rapid onset of action.[19] When doses above 0.25 μg/kg of fentanyl were used, a ceiling effect for the analgesia was observed, tolerance developed rapidly, and adverse effects occurred more frequently.[14] Additionally, the use of fentanyl was associated with a higher need for postoperative analgesics.

Although previous studies assessed the clinical advantages and risks of combining fentanyl with bupivacaine in spinal anesthesia for cesarean sections, the findings were highly controversial. Currently, there is no consensus on the optimal dose of fentanyl that should be combined with bupivacaine in spinal anesthesia for cesarean section deliveries. Additionally, the dose-response relationship for fentanyl combined with bupivacaine in spinal anesthesia for elective cesarean section deliveries has not been fully elucidated. Therefore, more studies were needed to inform decisions on the optimal dose of intrathecal fentanyl to be combined with bupivacaine that is needed to obtain an optimal mix of sensory and motor block, analgesia, and acceptable incidence of adverse effects. Additionally, few clinical studies were conducted in the Palestinian hospitals to inform obstetric practice on the optimal combination of local anesthetics and opioid analgesics for spinal anesthesia in cesarean section deliveries.

This prospective, randomized, double-blind clinical trial was conducted to determine the optimal dose of intrathecal fentanyl to be combined with bupivacaine that is needed to obtain an optimal mix of sensory and motor block, analgesia, and acceptable incidence of adverse effects in spinal anesthesia for cesarean section deliveries. In this study, sensory and motor block, analgesia, hemodynamic parameters, the incidence of adverse effects, and neonatal health outcomes were compared when bupivacaine alone or in combination with different doses of intrathecal fentanyl was used.

## 2. Methods

### 2.1. Study design

This study was conducted in a prospective, randomized, double-blind clinical trial in a gynecology and obstetrics department in one of the hospitals in the north of the West Bank of Palestine. The study was conducted in compliance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[20] Adherence to the CONSORT checklist is provided in Supplementary Table S1. The trial was registered in the Thai Clinical Trials Registry (TCTR). The study protocol was finalized prior to patient enrollment.

### 2.2. Study population, sample size, and recruitment

The study population was women with full-term pregnancies who were scheduled for cesarean delivery in the north of the West Bank of Palestine. The sample size for this randomized clinical trial was calculated using Pocock's formula, with a power of 80% and a significance level of 0.05. Based on an approximate duration of analgesia for bupivacaine and fentanyl, informed by previous studies.[21,22] The intended sample size for analysis was 160 participants (40 in each group) randomly allocated using the sealed envelope method, although recruitment extended beyond this figure to accommodate exclusions and unsuccessful spinal blocks. A greater number of patients were screened and randomized to guarantee that the final analyzed sample achieved the established aim.

The duration of analgesia was predetermined as the primary outcome variable for sample size estimation, as it signifies a clinically relevant endpoint directly associated with the study objective. Hemodynamic parameters and sensory block characteristics were incorporated as principal secondary efficacy and safety outcomes. The calculation was anchored to the primary pairwise comparison between the control group receiving bupivacaine alone (B10) and the group receiving bupivacaine combined with 25 μg fentanyl (F25), as this comparison was expected to yield the largest clinically meaningful difference. Estimates of the expected mean difference and standard deviation for duration of analgesia were informed by previously published randomized trials evaluating intrathecal fentanyl–bupivacaine combinations in cesarean delivery.[21,22] The sample size was determined to ensure sufficient power to identify clinically significant differences among the four study groups within an analysis of variance (ANOVA) framework, with equal distribution of participants (n = 40) per group. Consideration was given to the allowance for potential procedural exclusions; despite six failed spinal blocks occurring post-randomization, balanced group sizes were upheld, thus maintaining the intended statistical power.

The inclusion criteria used in this study were: 1) being at least 18 years old, 2) scheduled for elective cesarean sections at full-term pregnancy (at least 37 weeks gestation), 3) pregnant with a single fetus, 4) being scheduled for cesarean delivery under spinal anesthesia, 5) American Society of Anesthesiologists (ASA) physical class I and II, pregnancy is typically categorized as ASA II; however, women deemed otherwise healthy without systemic disease were classed as ASA I based on standard pre-anesthetic examination at the study location. The ASA physical status was uniformly distributed among all study groups and was not utilized as a stratification or outcome variable. And 6) providing written informed consent. Women who had a history of sensitivity/allergy to local anesthetics and opioids, psychiatric disorders, drug addiction, emergency cesarean deliveries, pregnancy complications, fetal distress, and/or those who could not provide written informed consent were excluded.

Before inclusion, all potential participants were assessed for eligibility against the inclusion and exclusion criteria. Laboratory tests were ordered, and women who had low platelet counts or had blood coagulation/bleeding disorders were excluded.

Participants were recruited using a consecutive (non-probability) sampling technique. All women scheduled for elective cesarean section at the study hospital during the recruitment period were consecutively assessed for eligibility based on predefined inclusion and exclusion criteria and were invited to participate until the target sample size was achieved.

### 2.3. Randomization and blinding

The Random Allocation Software for Windows (v.1.0) was used to generate random sequences for the women to be allocated to one of the 4 groups (40 women per group). The randomly generated allocation numbers were printed and placed into opaque sealed envelopes.

Randomization was performed using a computer-generated random sequence devised by an independent researcher who was not involved in patient recruitment or outcome evaluation. Allocation concealment was accomplished through the use of sequentially numbered, opaque, sealed envelopes that were pre-prepared and indistinguishable in appearance. Envelopes were opened in sequence following informed consent by an anesthesia technician not engaged in patient care or data collection, who prepared the study medications. Patients, anesthesiologists, surgeons, outcome evaluators, and data analysts remained unaware of group assignments during the study.

### 2.4. The intervention

The women had to fast, and preanesthetic drugs were not administered. In the operating theater, women were monitored continuously using ECG, pulse oximeter, and blood pressure monitoring. Venous access was obtained with an 18-gauge intravenous cannula. Preloading was conducted using a 0.9% sodium chloride solution in accordance with the research site's institutional protocols. All participants received the identical type and volume of intravenous fluid to maintain consistency among study groups. 0.9% NaCl (1000 cc) was infused over 40 min before the sensory block. Despite recommendations in

certain guidelines for obstetric anesthesia regarding balanced crystalloid solutions and routine premedication, this study did not administer any pharmacological premedication to prevent potential confounding effects on hemodynamic stability, block characteristics, and analgesic outcomes, which were the primary endpoints of the trial. The patient was positioned in the left lateral decubitus position. The lumbar area was meticulously disinfected, and the site was draped with a sterile towel. A 25-gauge Quincke spinal needle was carefully introduced at the L3–L4 interspace along the midline and advanced until entry into the subarachnoid space was confirmed by free cerebrospinal fluid (CSF) flow. Subsequently, the study drug was administered intrathecally over 30 seconds, with the needle bevel oriented cephalad.

After achieving sensory block, the women were placed in a supine position. The uterus was displaced to the left using an installed Crawford wedge, and the fetus was extracted. Women received oxygen supplementation at 6 L/min via a face mask throughout the procedure. Hypotension was treated with an intravenous bolus injection of Ringer's lactate solution and phenylephrine (40 μg), bradycardia was treated with intravenous atropine (0.5 mg), nausea was treated with intravenous metoclopramide (10 mg), and pain was treated with intravenous morphine (2.5 mg).

In this study, Group 1 received a 7.5 mg (1.5 mL) dose of 0.5% hyperbaric bupivacaine that was combined with 10 μg of fentanyl, Group 2 received a 7.5 mg (1.5 mL) dose of 0.5% hyperbaric bupivacaine that was combined with 15 μg of fentanyl, and Group 3 received a 7.5 mg (1.5 mL) dose of 0.5% hyperbaric bupivacaine that was combined with 25 μg of fentanyl. Preservative-free normal saline (0.9% NaCl) was added to the solutions prepared for the women in Groups 1-3 to make the final volume 2 mL. Group 4 received a dose of 10 mg (2 mL) 0.5% hyperbaric bupivacaine in 0.9% NaCl solution without fentanyl. Bupivacaine and fentanyl used to prepare the doses were from the same manufacturer.

All intrathecal study solutions were prepared under sterile conditions immediately prior to administration by an anesthesia technician uninvolved in patient care or outcome evaluation. For Groups 1–3, the designated fentanyl dosage (10, 15, or 25 μg) was extracted and amalgamated with 7.5 mg (1.5 mL) of 0.5% hyperbaric bupivacaine, with preservative-free 0.9% normal saline incorporated to attain a total intrathecal volume of 2 mL. For Group 4, 10 mg (2 mL) of 0.5% hyperbaric bupivacaine devoid of fentanyl was formulated. All study syringes were uniform in appearance and volume to ensure blinding was preserved.

### 2.5. The study variables

Data were gathered utilizing a standardized case report form specifically designed for this study. A version of the data gathering tool in English is included as Supplementary File S2.

The primary outcome was the duration of analgesia, and all other measured variables were considered secondary outcomes. In this study, the following variables were assessed: 1) sensory block latency, 2) duration of sensory block, 3) motor block latency, 4) duration of motor block, 5) duration of analgesia, 6) need for rescue analgesia, 7) self-reported satisfaction with the quality of analgesia, 8) systolic blood pressure, 9) heart rate, 10) need for vasopressors, 11) incidence of bradycardia, 12) incidence of nausea, 13) incidence of vomiting, 14) incidence of pruritus, 15) incidence of headache, 16) incidence of shivering, 17) incidence of drowsiness, and 18) Apgar scores. Additionally, age, weight, height, and duration of the cesarean surgery were also collected and compared.

Sensory block latency was defined as the time elapsed from the end of the spinal injection of the anesthetic solution and loss of pain sensation to the pinprick stimulus at the levels of thoracic 10 (T10) and T6. The sensory block latency was assessed every 15 sec using a pinprick stimulus with a blunt 27G needle at the center of the clavicular line. Motor block was assessed using the modified Bromage score as: null = can move the lower limbs freely, 1 = can flex the feet only, and 3 = cannot move the lower limbs. Duration of motor block was defined as the time elapsed from the end of the spinal injection of the anesthetic solution to the ability to freely move the lower limbs. The duration of analgesia was defined as the time elapsed from the end of the spinal injection of the anesthetic solution to the spontaneous self-reported sensation of pain as measured on the Visual Numeric Scale (VNS) ($\geq$3). Satisfaction with the quality of analgesia was self-reported by the patients as: 1) excellent (no complaints), 2) Good (minor discomfort with no need for additional analgesics), 3) fair (moderate discomfort with a need for additional analgesics), and 4) Poor (high discomfort requiring rescue analgesia or conversion due to inadequate spinal anesthesia). For analytical purposes, responses were categorized into 'satisfactory' (excellent/good) and 'unsatisfactory' (fair/poor) to enable clinically significant interpretation and statistical comparison between groups. In cases of intraoperative discomfort or inadequate spinal block, rescue analgesia was administered using intravenous medications according to institutional practice. Cases requiring conversion to an alternative anesthetic technique were classified as failed spinal blocks. Satisfaction was evaluated as a patient-reported outcome using a predetermined four-level ordinal scale, administered in a standardized manner; analgesic adequacy was further corroborated by objective indicators, including analgesia duration and the need for rescue analgesics.

Systolic blood pressure and heart rate were measured at 2, 4, and 6 min into the surgery. Neonatal health was assessed using the appearance, pulse rate, grimace Reflex irritability, activity, and respiratory effort (Apgar) scores at 1- and 5-min.

Incidence of bradycardia, nausea, vomiting, pruritus, headache, shivering, and drowsiness was recorded as dichotomous variables (yes/no).

### 2.6. Statistical analysis

The data collected in this study were entered into GraphPad Prism v.7.0 (GraphPad Software, San Diego, CA). Continuous data were expressed as mean ± standard deviation (SD). Dichotomous data were expressed as numbers and percentages. The continuous data were compared using analysis of variance (ANOVA) with Tukey's multiple-comparison test. The dichotomous data were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was considered as * when the p-value was $< 0.05$, ** when the p-value was $< 0.01$, *** when the p-value was $< 0.001$, and **** when the p-value was $< 0.0001$.

The principal endpoint of this trial was the duration of effective postoperative analgesia, defined as the period from the completion of the intrathecal injection to the first need for rescue analgesia (VNS $\geq 3$). This result was preordained to correspond with the principal clinical objective of enhancing intrathecal fentanyl administration during elective cesarean section. Secondary outcomes included the latency and duration of sensory and motor block, intraoperative hemodynamic parameters, incidence of adverse effects, mother satisfaction, and neonatal Apgar scores. Continuous variables were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparison test to account for pairwise comparisons. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The criterion for statistical significance was set at $p < 0.05$.

Comparisons among the four study groups were initially conducted using one-way analysis of variance (ANOVA). When overall group differences were statistically significant, post-hoc pairwise comparisons were conducted using Tukey's honest significant difference (HSD) test to control for type I error inflation due to multiple comparisons. The principal outcome (duration of analgesia) was evaluated in a confirmatory manner, as it served as the basis for the sample size calculation. Examinations of secondary outcomes were deemed exploratory.

### 2.7. Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1975, as revised in 2024. The study received ethical approval from the Institutional Review Board (IRB) of An-Najah National Ministry of Health (Approval No. Med.2024/3518) and the Palestinian Ministry of Health. Written informed consent was obtained from each participant prior to enrollment.

## 3. Results

Continuous variables are expressed as mean ± standard deviation (SD) in supplementary tables unless specified otherwise.

### 3.1. Participants

In this study, 190 women were screened for eligibility. Of those, 24 were excluded, and 166 were randomized into the 4 groups. Of the patients included, spinal block failed in 6 patients. Data from 40 women in each group (total = 160) were included in the final analysis. The final analysis was performed on a per-protocol basis, encompassing only participants who achieved successful spinal anesthesia. Six randomized participants experienced unsuccessful spinal blocks before the outcome assessment and were excluded from the efficacy analysis per protocol, as no significant anesthetic or analgesic outcomes could be evaluated. CONSORT flow diagram showing screening (n = 190), exclusions prior to randomization (n = 24), randomization (n = 166), exclusions due to failed spinal anesthesia (n = 6), and final analysis (n = 160. (Figure 1).

## 4. Consort flow diagram of participant recruitment

### 4.1. Demographic and procedural variables

There were no statistically significant differences (p-value > 0.05) in age, weight, height, or ASA status among the women allocated to the 4 groups (Figures 2(A)–(C)). Similarly, there was no statistically significant difference (p-value > 0.05) in the duration of cesarean surgery performed on the women allocated to the 4 groups (Figure 2(D)).

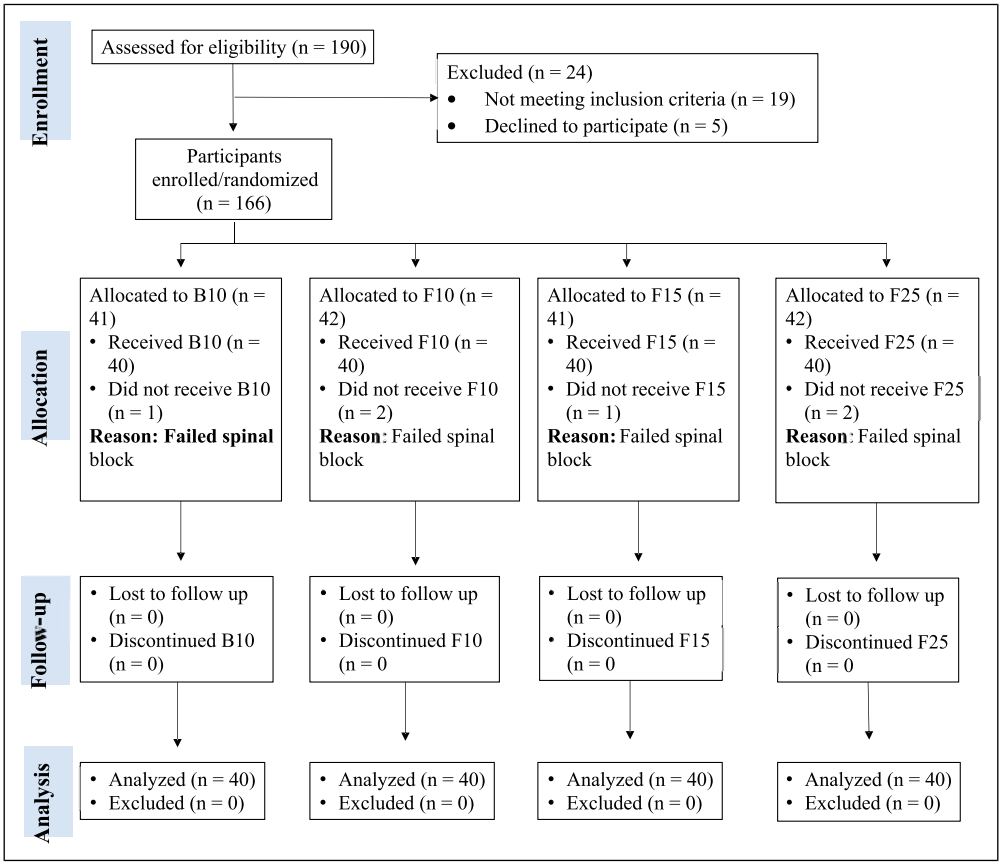


**Figure 1.** CONSORT flow diagram of participant recruitment.

### *4.2. Sensory and motor block*

The sensory block latency at the T10 level was significantly shorter (p-value $< 0.0001$) when fentanyl was combined with bupivacaine compared to bupivacaine alone (Figure 3(A)). Additionally, there was a statistically significant gradual decrease in the sensory block latency at the T10 level when the dose of the combined fentanyl was increased from 10 μg (F10) to 15 μg (F15) and 25 μg (F25) (Figure 3(A)). Similarly, the sensory block latency at the T6 level was significantly shorter (p-value $< 0.0001$) when fentanyl was combined with bupivacaine compared to bupivacaine alone (Figure 3(B)). However, the sensory block latency at the T6 level did not differ (p-value $> 0.05$) when the dose of the combined fentanyl was increased from 15 μg (F15) to 25 μg (F25).

Similarly, the duration of sensory block was significantly longer (p-value $< 0.0001$) when fentanyl was combined with bupivacaine compared to bupivacaine alone (Figure 3(C)). Additionally, there was a statistically significant gradual increase in the sensory block duration when the dose of the combined fentanyl was increased from 10 μg (F10) to 15 μg (F15) and 25 μg (F25) (Figure 3(C)).

On the other hand, the motor block latency was significantly shorter (p-value $< 0.0001$) when bupivacaine was used alone compared to bupivacaine combined with fentanyl (Figure 3(D)). Additionally, there was a statistically significant gradual decrease in motor block latency with increasing combined fentanyl dose from 10 μg (F10) to 15 μg (F15) and 25 μg (F25) (Figure 3(D)). Similarly, the duration of motor block was significantly longer (p-value $< 0.0001$) when bupivacaine was used alone compared to bupivacaine combined with fentanyl (Figure 3(E)). The duration of the motor block was significantly shorter (p-value $< 0.0001$) for combined fentanyl 10 μg (F10) and 15 μg (F15) compared to combined fentanyl 25 μg (F25) (Figure 3(E)).

### *4.3. Duration, degree, and quality of analgesia*

The duration of analgesia was significantly longer (p-value $< 0.0001$) when fentanyl was combined with bupivacaine compared to bupivacaine alone (Figure 4(A)). Similarly, there was a statistically significant gradual increase (p-value $< 0.0001$) when the dose of fentanyl was increased in the combination from 10 to 15 and 25 μg. In this study, less rescue analgesia was needed when bupivacaine was combined with 25 μg of fentanyl (p-value $< 0.0001$) compared to bupivacaine alone (B10), bupivacaine combined with 10 μg of fentanyl (F10), and bupivacaine combined with 15 μg of fentanyl (F15) (Figure 4(B)).

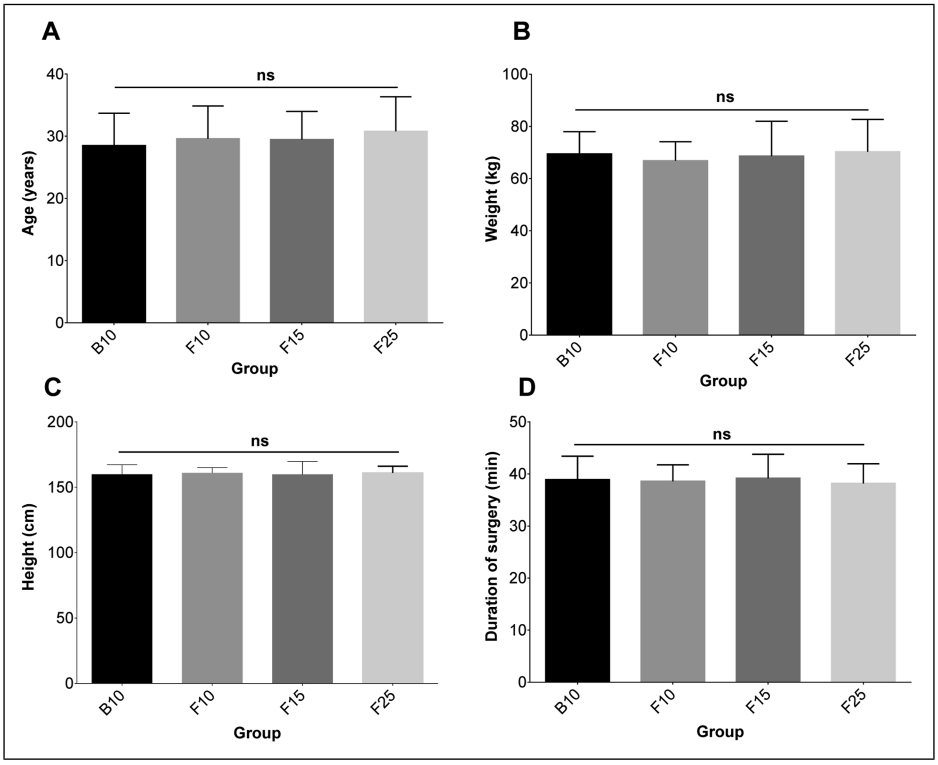


**Figure 2.** Comparison between age (A), weight (B), height (C), and duration of the cesarean surgery (D) in the 4 groups. Ns: the p-value was not significant.

When asked to express the degree of their satisfaction with the quality of analgesia, satisfaction views were expressed by the women who received bupivacaine combined with fentanyl (p-value < 0.001). There was a statistically significant gradual increase in the expressed satisfaction with analgesia quality when the combined fentanyl dose was increased from 10 μg (F10) to 15 μg (F15) and 25 μg (F25) (Table 1).

### 4.4. Intraoperative hemodynamic stability

The systolic blood pressure was significantly lower (p-value < 0.0001) when bupivacaine was used alone compared to bupivacaine combined with fentanyl at 2, 4, and 6 minutes through the cesarean surgery (Figure 5(A)). Similarly, the heart rate was significantly lower when bupivacaine was used alone compared to bupivacaine combined with fentanyl at 2, 4, and 6 minutes through the cesarean surgery (Figure 5(B)). Additionally, the frequency of need for vasopressors was significantly higher (p-value < 0.0001) when bupivacaine was used alone compared to bupivacaine combined with fentanyl at 2, 4, and 6 minutes through the cesarean surgery (Figure 5(C)).

### 4.5. Incidence of adverse effects

More episodes of bradycardia and vomiting were reported when bupivacaine was used alone compared to bupivacaine combined with fentanyl (Table 2). On the other hand, more episodes of pruritus were reported when bupivacaine was combined with fentanyl compared to bupivacaine alone (p-value < 0.01). There were no statistically significant differences in headache, shivering, nausea, or drowsiness among the 4 groups (p-values> 0.05).

### 4.6. Newborn's health

There were no statistically significant differences in the 1- and 5-min Apgar scores measured for the babies born to the women allocated to the 4 groups (Figures 6(A) and (B)). Comprehensive distributions of Apgar scores at 1 and 5 minutes are available in the Supplementary Material (Tables S5 and S6).

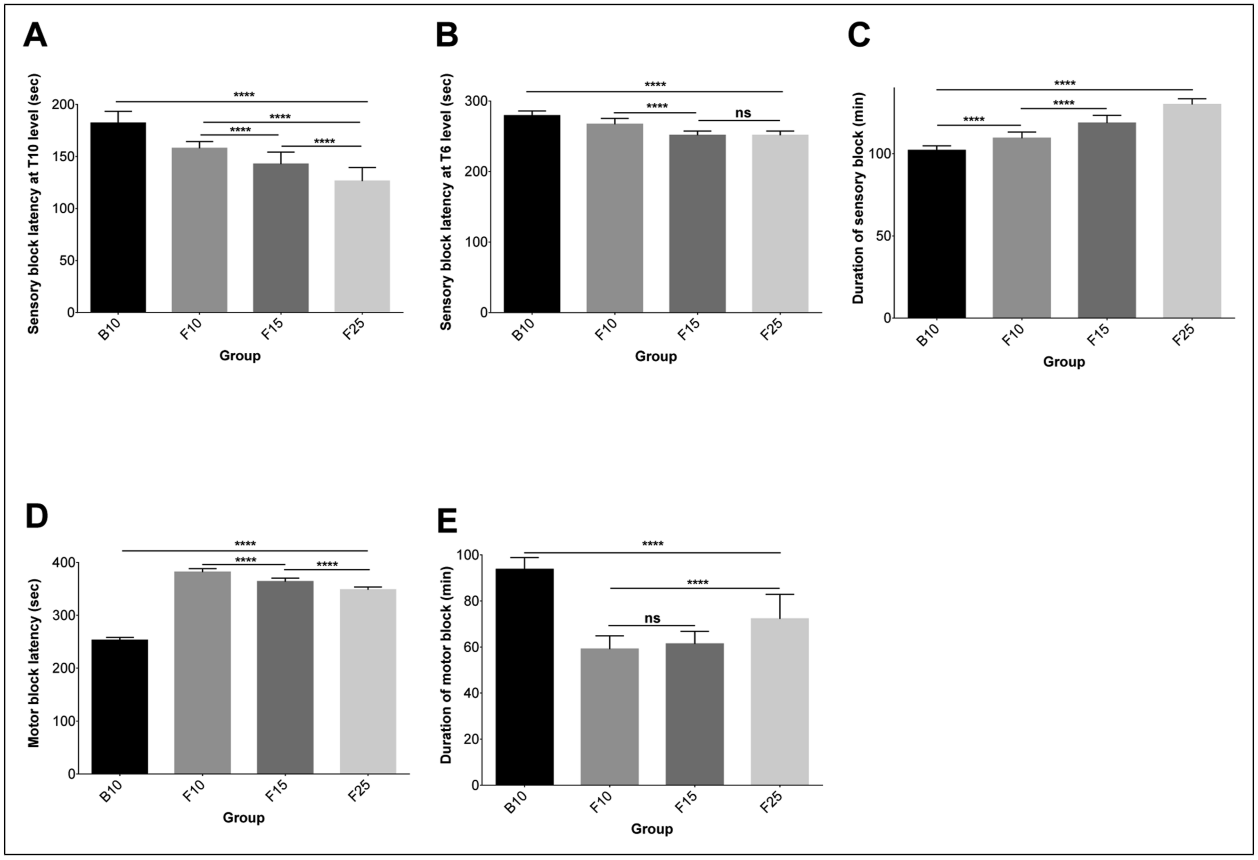


**Figure 3.** Sensory and motor block. **** when the p-value was < 0.0001, ns when the p-value was not significant.

## 5. Discussion

With the increasing number of women opting for planned deliveries, elective cesarean sections are becoming increasingly common in today's obstetrics practice.[1–5] It is therefore important to provide safe and adequate anesthesia and analgesia for those women for a successful cesarean section delivery. In this study, variables related to the adequacy of the sensory and motor block, quality of analgesia, hemodynamic stability, the incidence of adverse effects, and neonatal outcomes were

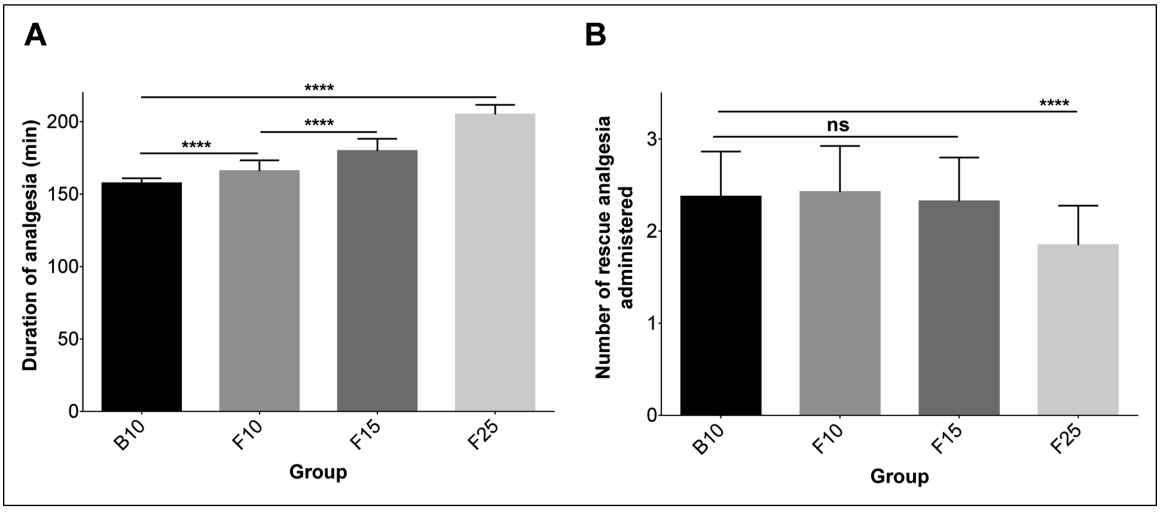


**Figure 4.** Duration of analgesia (A) and number of rescue analgesia administered (B). **** when the p-value was < 0.0001, ns when the p-value was not significant.

**Table 1.** Satisfaction with the quality of analgesia.

| Group | Unsatisfaction | | Satisfaction | | Pearson Chi-Square/Fisher's exact test | p-value |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| B10 | 32 | 80.0 | 8 | 20.0 | 41.79 | < 0.001 |
| F10 | 27 | 67.5 | 13 | 32.5 | | |
| F15 | 23 | 57.5 | 17 | 42.5 | | |
| F25 | 5 | 12.5 | 35 | 87.5 | | |

compared when spinal anesthesia was performed using hyperbaric bupivacaine alone and in combination with different doses of intrathecal fentanyl. The study aimed at finding the optimal dose of fentanyl in combination with bupivacaine to achieve a balanced sensory and motor block, a high level of analgesia, and a minimal level of adverse effects. The findings of this study would be informative to planners of elective cesarean sections in the Palestinian obstetrics practice.

While the analgesic and hemodynamic effects of intrathecal fentanyl combined with bupivacaine for cesarean delivery have been thoroughly examined, most previous randomized trials and systematic reviews have concentrated on its application alongside standard doses of local anesthetics. Prior research has shown enhanced analgesic efficacy and dose-dependent adverse effects when intrathecal fentanyl is incorporated into standard-dose spinal anesthesia for cesarean delivery, as evidenced by both randomized trials and observational studies[23,24]. Moreover, recent systematic reviews and meta-analyses have consolidated this evidence and validated the analgesic advantages of intrathecal fentanyl, while emphasizing dose-dependent adverse effects, notably pruritus.[25]

This study specifically assessed the optimization of fentanyl dosage within a low-dose spinal anesthesia technique. In this context, the equilibrium between attaining sufficient surgical anesthesia, extending postoperative analgesia, and reducing opioid-related side effects may significantly vary from standard-dose methodologies. Our findings indicate that a 25 μg intrathecal fentanyl dose, in conjunction with a reduced dose of bupivacaine, offers the optimal balance of analgesic efficacy, block characteristics, and side-effect profile, thereby endorsing dose-sparing spinal anesthesia strategies for elective cesarean delivery.

In this study, combining doses of fentanyl with bupivacaine significantly shortened the sensory block latency and significantly increased the duration of the sensory block. The sensory block latency at the T10 level gradually decreased, and the duration of the sensory block significantly increased with the increasing dose of fentanyl. The findings reported in this study were consistent with those of previous studies in which doses of fentanyl also shortened the sensory block latency and increased the duration of sensory block.[14,21,26–28] Similarly, combining doses of fentanyl with bupivacaine significantly shortened the sensory block latency at the T6 level. However, when the dose of the combined fentanyl was increased from 15 to 25 μg, there was no significant further decrease in the sensory block latency at the T6 level. This might indicate a ceiling effect of fentanyl, as was reported in previous studies.[14,21] Although the motor block latency was significantly shorter and the duration of the motor block was significantly longer when bupivacaine alone was used, the motor block latency was significantly shorter, and the duration of the motor block was significantly longer when an intrathecal dose of 25 μg of fentanyl was combined with bupivacaine compared to doses of 10 and 15 μg. The findings of this study were consistent with

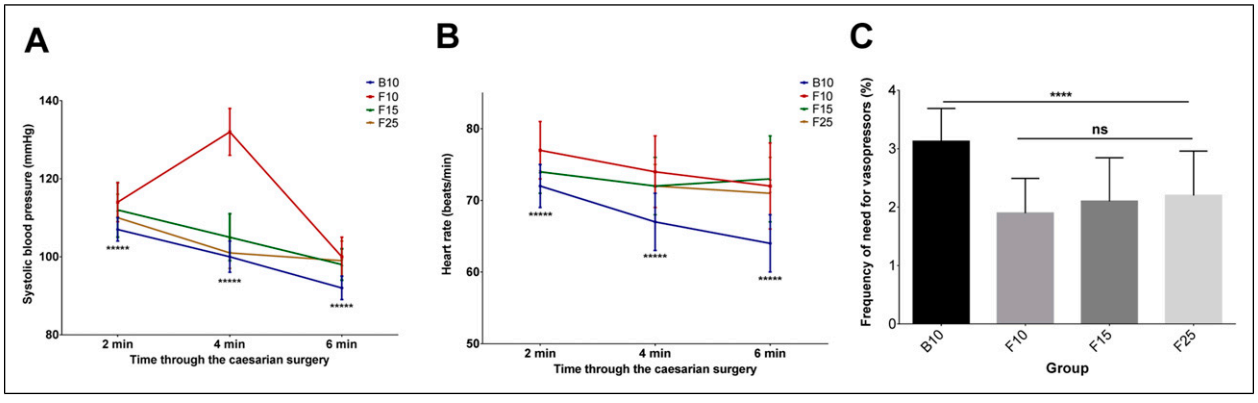


**Figure 5.** Systolic blood pressure (A), heart rate (B), and frequency of needed vasopressors (C). **** when the p-value was < 0.0001, ns when the p-value was not significant.

**Table 2.** Adverse effects reported among the patients in the 4 groups.

| Effect | Group | No | | Yes | | Pearson Chi-Square/Fisher's exact test | p-value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| Bradycardia | B10 | 35 | 87.5 | 5 | 12.5 | 10.01 | 0.017 |
| | F10 | 40 | 100.0 | 0 | 0.0 | | |
| | F15 | 40 | 100.0 | 0 | 0.0 | | |
| | F25 | 38 | 95.0 | 2 | 5.0 | | |
| Headache | B10 | 31 | 77.5 | 9 | 22.5 | 5.04 | 0.185 |
| | F10 | 37 | 92.5 | 3 | 7.5 | | |
| | F15 | 36 | 90.0 | 4 | 10.0 | | |
| | F25 | 37 | 92.5 | 3 | 7.5 | | |
| Pruritus | B10 | 39 | 97.5 | 1 | 2.5 | 9.75 | 0.019 |
| | F10 | 38 | 95.0 | 2 | 5.0 | | |
| | F15 | 34 | 85.0 | 6 | 15.0 | | |
| | F25 | 31 | 77.5 | 9 | 22.5 | | |
| Shivering | B10 | 33 | 82.5 | 7 | 17.5 | 6.30 | 0.090 |
| | F10 | 39 | 97.5 | 1 | 2.5 | | |
| | F15 | 38 | 95.0 | 2 | 5.0 | | |
| | F25 | 38 | 95.0 | 2 | 5.0 | | |
| Nausea | B10 | 32 | 80.0 | 8 | 20.0 | 7.24 | 0.060 |
| | F10 | 39 | 97.5 | 1 | 2.5 | | |
| | F15 | 37 | 92.5 | 3 | 7.5 | | |
| | F25 | 34 | 85.0 | 6 | 15.0 | | |
| Vomiting | B10 | 35 | 87.5 | 5 | 12.5 | 9.56 | 0.003 |
| | F10 | 40 | 100.0 | 0 | 0.0 | | |
| | F15 | 40 | 100.0 | 0 | 0.0 | | |
| | F25 | 40 | 100.0 | 0 | 0.0 | | |
| Drowsiness | B10 | 39 | 97.5 | 1 | 2.5 | 2.82 | 1.000 |
| | F10 | 40 | 100.0 | 0 | 0.0 | | |
| | F15 | 40 | 100.0 | 0 | 0.0 | | |
| | F25 | 40 | 100.0 | 0 | 0.0 | | |

those reported in previous studies.[21,26–28] Taken together, these findings indicate that combining a dose of 25 μg of fentanyl with bupivacaine provided the optimal mix of sensory and motor block for cesarean section delivery.

The findings of this study indicated that the optimal analgesia was obtained when a 25 μg dose of fentanyl was combined with bupivacaine compared to bupivacaine alone or combined with lower doses of fentanyl. The optimal analgesia produced

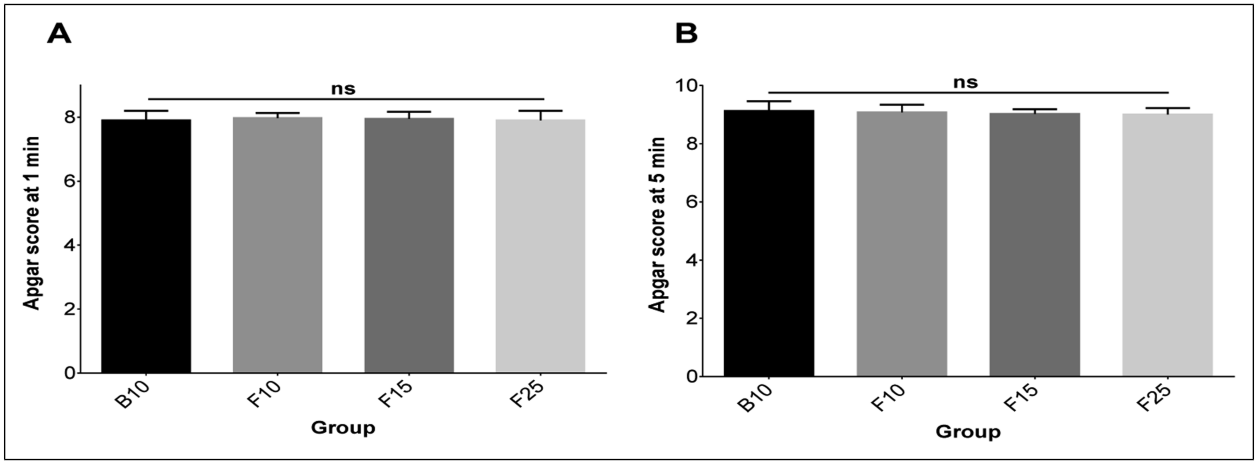


**Figure 6.** Apgar scores at 1 min (A) and at 5 min (B). Ns when the p-value was not significant Detailed descriptive statistics (mean ± standard deviation) and effect size estimates with corresponding 95% confidence intervals for the primary and key secondary outcomes are provided in the Supplementary Material (Tables S3–S4).

by the 25 μg dose of fentanyl was indicated by the significantly longer duration, less need for rescue analgesia, and more women rating the quality of analgesia as satisfactory. These findings were not surprising as fentanyl is a potent opioid analgesic, and when combined with bupivacaine, fentanyl is expected to have clinical benefits in reducing visceral pain that is associated with the intraoperative peritoneal traction in cesarean section delivery.[14,26]

In this study, the systolic blood pressure and heart rate were significantly lower when bupivacaine alone was used. Similarly, more vasopressors were administered when bupivacaine alone was used. When used alone, higher doses of bupivacaine will be needed to produce a satisfactory level of spinal anesthesia and an acceptable level of analgesia. Such high doses have previously been shown to be associated with hemodynamic instabilitynd a higher incidence of bradycardia and hypotension.[12,14,15,29] Similarly, more episodes of vomiting were reported among the women who received bupivacaine alone. These findings were consistent with those reported in previous studies.[27,29,30] Combining fentanyl with bupivacaine was previously proposed as a strategy to reduce the incidence of hemodynamic instabilities and vomiting associated with using bupivacaine alone in spinal anesthesia for cesarean sections.[12,15] Although the findings of this study showed that the incidence of bradycardia was higher among the women who received 25 μg fentanyl compared to those who received lower doses of fentanyl (10 and 15 μg), the incidence of bradycardia was significantly higher among the women who received bupivacaine alone. Taken together, these findings might indicate that combining fentanyl with bupivacaine can improve hemodynamic stability and reduce the need for antiemetic drugs compared to bupivacaine alone in spinal anesthesia for cesarean sections.

The women who received fentanyl combined with bupivacaine reported more episodes of pruritus compared to those who received bupivacaine. More episodes of pruritus were reported among the women who received 25 μg fentanyl. The findings of this study were consistent with those reported in previous studies.[14,21,27] Previous studies have shown that pruritus was associated with the use of opioid analgesics. Although pruritus is not a serious or life-threatening condition, it can cause discomfort and can affect the patient's satisfaction.[31] Severe cases of pruritus can be managed with opioid receptor antagonists like naloxone.

Recent randomized trials and meta-analyses have validated the analgesic efficacy of intrathecal fentanyl, while also emphasizing dose-dependent adverse effects, including pruritus[23–25]**.** The current findings augment this evidence by indicating that, within a low-dose spinal anesthesia context, increased fentanyl dosages may be required to maintain analgesic efficacy without jeopardizing hemodynamic stability.

In this study, neither bupivacaine alone nor bupivacaine combined with the different doses of fentanyl affected the neonatal outcomes as indicated by the Apgar scores. The findings of this study were consistent with those reported in previous studies.[12,14,21,29]

### *5.1. Strengths and limitations of the study*

The findings reported in this study should be interpreted considering some strengths and limitations. First, this study was conducted in a prospective, randomized, double-blind design. Findings from prospective, randomized, double-blind clinical trials are superior to those from retrospective, non-randomized, and open-label trials. Second, this study was conducted in adherence to the CONSORT guidelines. Adherence to the international guidelines can promote transparency and congruence in reporting results. This can subsequently promote comparability between the findings reported in different settings. Third, the sample size used in this study was adequate, and the number of women allocated to each group was similar.

Additionally, the age, weight, height, and duration of the cesarean section were similar in the 4 groups. This should have enabled better control of confounders and promoted comparison of the other clinical variables across the 4 groups. Fourth, different doses of fentanyl were assessed in this study. The high dose range used in this study should have promoted identifying the optimal dose of fentanyl to be combined with bupivacaine. Fifth, in addition to the maternal variables, neonatal health outcomes were also collected and compared among the 4 groups in this study. This should have added more strength and depth to the findings of this study.

On the other hand, the findings of this study should be interpreted in light of several limitations. First, this was a single-center trial conducted at a single hospital in Palestine, which may limit the generalizability of the results to other populations and healthcare systems. Second, although the sample size (160 women) was adequate for the primary analysis, it did not allow for subgroup analyses (e.g., age, parity, comorbidities). Third, outcomes were limited to the immediate perioperative and short-term postoperative period; we did not evaluate long-term maternal or neonatal outcomes. Fourth, satisfaction with analgesia quality was self-reported, which could be influenced by subjective perceptions and introduce reporting bias. Fifth, adverse effects were measured as dichotomous variables (yes/no); using a graded severity scale would have provided more nuanced information. Sixth, neonatal outcomes were limited to 1- and 5-minute Apgar scores, which may not fully reflect neonatal well-being; additional assessments could have strengthened the findings. Finally, the trial was retrospectively registered, which may raise concerns about prospective transparency, although all procedures were conducted in accordance

with ethical approvals and CONSORT guidelines. Despite the ICMJE criteria recommending prospective registration, this trial was registered retroactively owing to local administrative and logistical limitations at the study's commencement. The comprehensive study protocol—encompassing objectives, eligibility criteria, outcome measures, randomization procedures, and statistical analysis plan was completed and sanctioned by the Institutional Review Board of An-Najah National University and the Palestinian Ministry of Health prior to the enrollment of the initial participant. No modifications were made to the study design, outcomes, or analyses after recruitment commenced, and all predetermined outcomes are documented in the publication. We see retrospective registration as a constraint and have implemented measures to guarantee complete transparency. Upcoming clinical trials undertaken by our team will be prospectively recorded in compliance with international standards.

In addition, a significant methodological limitation of this study is that the group comparison entailed two concurrent modifications: the introduction of intrathecal fentanyl and a decrease in the hyperbaric bupivacaine dosage from 10 mg to 7.5 mg. Thus, the enhanced hemodynamic stability noted in the fentanyl groups cannot be exclusively ascribed to the opioid effect, since diminished doses of bupivacaine are independently linked to a decreased occurrence of spinal-induced hypotension. The addition of a 7.5 mg bupivacaine-only cohort would have facilitated a more distinct evaluation of fentanyl's independent effect; however, this cohort was omitted due to clinical and ethical considerations. Prior evidence indicates that minimal doses of intrathecal bupivacaine, administered without an opioid adjunct, correlate with an elevated risk of insufficient sensory blockade, intraoperative visceral pain, and the necessity for additional analgesia or transition to general anesthesia during cesarean delivery.[32] Nonetheless, the dose-response relationship identified among the fentanyl groups, all administered the identical bupivacaine dosage, substantiates the auxiliary role of intrathecal fentanyl in improving block characteristics and analgesic results. Future research should include a low-dose bupivacaine-only control group, where ethically permissible, to clarify the independent effects of intrathecal opioids.

Despite the trial registry identified hemodynamic variables and sensory block delay as key endpoints, whereas the duration of analgesia was designated as a secondary outcome. Sample size estimation was predicated on the duration of analgesia, given its anticipated impact size and clinical significance in evaluating intrathecal opioid dose optimization. This mismatch indicates variations in result categorization rather than retrospective outcome selection and should be interpreted accordingly.

## 6. Conclusion

This study suggests that incorporating fentanyl into bupivacaine for spinal anesthesia during elective cesarean sections may offer clinical advantages. The combination of 25 μg intrathecal fentanyl with 7.5 mg of 0.5% hyperbaric bupivacaine was associated with a favorable balance of sensory blockade, motor blockade, analgesia, and side effects compared with bupivacaine alone or lower fentanyl doses. However, the increased incidence of pruritus should be considered, and further research is needed to confirm these findings.

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### Ethical considerations

This study was conducted in adherence to the principles of the Declaration of Helsinki. The study received ethical approval from the Institutional Review Board (IRB) of An-Najah National University. The study was also approved by the Palestinian Ministry of Health's ethics committee.

### Consent to participate

Written informed consent was obtained from all women before they participated in the study.

## Author contributions

AA and NA were involved in the conception and design of the work, analysis and interpretation of data, drafting, and final approval of the manuscript. AA, NA, and AY were involved in data acquisition, analysis, and the drafting of the work, and in the final approval of the version to be published. NS and MH were involved in the drafting of the work and the final approval of the version to be published.

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## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Trial registration

The trial was retrospectively registered in the Thai Clinical Trials Registry (TCTR). TCTR20220430008. Registered 30 April 2022.

## Supplemental material

Supplemental material for this article is available online.

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