

ORIGINAL RESEARCH

OBSTETRIC ANESTHESIA

Intrathecal midazolam is a comparable alternative to fentanyl and nalbuphine as adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: a randomized controlled double-blind trial

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Abstract

Background: Different adjuvants have been introduced to enhance the quality of local anesthetics and reduce its adverse events. This study was directed to compare the anesthetic and analgesic properties of intrathecal hyperbaric bupivacaine when three different adjuvant drugs were added.

Methodology: One hundred full-term parturients aged 18 to 40 years, scheduled for elective cesarean section, were randomly assigned to 4 groups. Each group received 12.5 mg of 0.5% hyperbaric bupivacaine combined with either 0.5 ml saline (Group-B), 25µg fentanyl (Group-F), 0.8 mg nalbuphine (Group-N) or 2 mg midazolam (Group-M). The outcomes included the postoperative effective analgesia time, the sensorimotor characteristics, postoperative VAS score, pethidine consumption, maternal complications, and neonatal Apgar score.

Results: Earlier onset of sensory and motor block was observed in Group F and N than in Group B and M. Duration of postoperative effective analgesia was longer in Groups F, N and M (252.42 ± 46.11 , 227.34 ± 36.54 and 243.71 ± 44.95 hours, respectively) than in Group B (172.11 ± 20.99) ($P < 0.001$). VAS scores decreased in adjuvant groups during the first 12 hours postoperative and required pethidine doses were less.

Conclusion: Addition of adjuvant agents to intrathecal bupivacaine improved the quality of subarachnoid block without increasing side-effects. Intrathecal midazolam provided comparable outcomes as the frequently used opioids.

Abbreviations: CS: Cesarean section; LA: Local anesthetics; SA: Spinal anesthesia

Key words: Intrathecal; Nalbuphine; Midazolam; Fentanyl; Postoperative analgesia; Cesarean section.

Citation: Amin SR, Souidan I, Abdelzaam EM. Intrathecal midazolam is a comparable alternative to fentanyl and nalbuphine as adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: a randomized controlled double-blind trial. *Anaesth. pain intensive care* 2022;27(1):89–96; DOI: [10.35975/apic.v27i1.1923](https://doi.org/10.35975/apic.v27i1.1923)

Received: June 26, 2022; **Reviewed:** November 28, 2022; **Accepted:** December 14, 2022

1. Introduction

Cesarean section (CS) is one of the most regularly conducted procedures in women, and spinal anesthesia

(SA) is the intervention of choice to manage it. SA is safe, simple to apply, effective and inexpensive. It avoids aspiration pneumonia and has a low failure rate and high maternal satisfaction. The main drawback of SA is its short duration of action when it is conducted with local

anesthetics (LA) alone. Therefore, intrathecal adjuvants were proposed to improve the quality of SA by prolonging its anesthetic and analgesic effect and to decrease the amount of LA used and the systemic analgesics needed postoperatively.¹

The most often used intrathecal adjuvants are opioids, which have been shown to improve the quality of neuraxial anesthesia. Intrathecal opioids produce segmental analgesia through attaching to opioid receptors present in the spinal cord dorsal horn. Opioids also have sympathetic and motor nerve sparing activity that extends analgesia without interfering with patient ambulation.²

Fentanyl, a short-acting lipophilic μ -receptor agonist, was acknowledged to enhance the quality of SA in various trials. However, its use is restricted due to concerns about its side effects including, nausea/vomiting, urine retention, pruritus and respiratory depression.³

Nalbuphine, a synthetic opioid acting on both μ - and κ receptors, has a mixed agonist-antagonist activity. It competitively binds to μ -receptors and displaces other μ -agonists from their receptors without stimulation, thus reducing the adverse events related to μ -agonists. However, when nalbuphine binds to κ receptors, which are distributed all over the brain and spinal cord, it produces agonist effect (analgesia).⁴

Midazolam is a short-acting benzodiazepine having antianxiety, anticonvulsant, amnesic and antiemetic properties. Intrathecal midazolam produces segmental analgesia through binding to benzodiazepine–gamma aminobutyric acid (GABA) receptor complex that are spread in the spinal cord gray matter. Previous studies have demonstrated the effect of intrathecal midazolam in improving the quality and duration of SA.⁵

Since midazolam is a widely accessible and inexpensive medication with multiple effects, we hypothesized that midazolam would prolong the anesthetic and analgesic action of intrathecal hyperbaric bupivacaine equivalent to the opioid adjuvants. Based on this assumption, we compared the efficacy of intrathecal midazolam in contrast to fentanyl and nalbuphine in hyperbaric bupivacaine in parturients undergoing elective CS.

2. Methodology

Following approval of the Institutional Ethical Committee (No. RC-6-5-2021) this prospective randomized controlled double-blinded study was performed at Benha University Hospital from June 2021 to April 2022. This trial was prospectively registered in the clinicaltrials.gov (No. NCT04932083).

The study included one hundred parturients, aged 18 to 40 y, ASA physical status II, scheduled for elective CS under SA. Participants were assigned randomly into four groups, via a computer-generated list number. Written informed consents were obtained from all of the participants.

The exclusion criteria were ASA grade III/IV, refusal of SA, physical dependency on opiates or benzodiazepine, allergy history to any of used adjuvants, localized skin infection, significant spinal deformity, bleeding disorder or neurological disease, incapability to communicate, morbid obesity, Complicated pregnancy, and failed spinal blockade. During the preoperative clinical evaluation, eligible parturients were instructed to use the 10 cm visual analog scale (VAS) for determining the intensity of pain. On the scale, 0 point indicates “no pain” and 10 points indicate “worst pain”.

The assignments were placed in opaque envelopes and unsealed by an anesthetic nurse, who prepared the study mixtures with total volume of 3 ml in each group as follow:

Group-B: 2.5 ml of 0.5% hyperbaric bupivacaine (12.5 mg) + 0.5 ml saline.

Group-F: 2.5 ml of 0.5% hyperbaric bupivacaine (12.5 mg) + 0.5 ml fentanyl (25 μ g).

Group-N: 2.5 ml of 0.5% hyperbaric bupivacaine (12.5 mg) + 0.8 mg nalbuphine in 0.5 ml sterile water.

Group-M: 2.5 ml of 0.5% hyperbaric bupivacaine (12.5 mg) + 0.4 ml of midazolam (2 mg) + 0.1 ml of sterile water.

Peripheral intravenous access (18G cannula) was secured in the operating room. Blood pressure, ECG, and SpO₂ baseline values were recorded. Before SA, each parturient was given 15 ml/kg of Ringer's lactate solution as preload. An anesthesiologist who was not engaged in the intrathecal mixture formulation performed a dural puncture at L3–L4 interspace with a 25G spinal needle in sitting position under aseptic conditions. The parturient and the anesthetist who was responsible for collecting the outcome data, were blinded to the tested spinal medication.

After injecting the study mixture, the parturient was placed supine with a 15-degree wedge below the right hip for left displacement of uterus. Oxygen (3 L/min) was delivered through a facemask. Cardio-respiratory variables including heart rate, non-invasive blood pressure, SpO₂ and ECG were monitored.

Intraoperative hypotension was considered when mean arterial blood pressure was < 60 mmHg and was managed with 5 mg ephedrine bolus dose and fluids. Bradycardia (heart rate < 50 beats/min) was treated with

atropine 0.5 mg increments. Vomiting was managed with 10 mg metoclopramide or 1 mg granisetron if resistant. Diphenhydramine 25 mg was used to treat pruritus and pethidine 25 mg was used for shivering.

Sensory block onset time was defined as the time from intrathecal injection to disappearance of pain sensation at (T5) dermatome. Duration of complete sensory block was the time interval from intrathecal block until first pain sensation. Time to 2-segments regression was the time interval from intrathecal injection until regression of sensory level by 2-segments from the highest dermatomal block level. The loss of sensation was examined by using a pinprick test at the mid-clavicular line on each side every 2 min for 10 min, every 5 min for the following 20 min, and then examined every 15 min until 2-segments regression occurred from the highest level.

Motor block onset time was defined as the time from intrathecal injection until Bromage score 3. Duration of motor block was the time interval from intrathecal injection till Bromage score 0. The motor blockade was evaluated using Bromage scale: 0 = can do flexion to an extended leg at hip joint, 1 = can't flex extended leg but can flex knee, 2 = can move only foot, 3 = can't move her foot. It was checked every 2 min for 10 min and then every 15 min until the score returned zero.

Effective analgesia duration was defined as the time from intrathecal block until first analgesic requirement (VAS > 3). For rescue analgesia, 30 mg ketorolac was injected intravenously and repeated after 6 h if necessary. After 20 min from ketorolac administration, if the VAS > 3 pethidine 0.5 mg/kg was given IV. Total pethidine consumed was noted.

VAS pain scores were evaluated at 3, 6, 9, 12, 18 and 24 h postoperatively. Parturients were observed for any associated side-effects including hypotension, bradycardia, pruritus, shivering, postoperative nausea/vomiting (PONV), post-spinal headache and respiratory depression.

The six-point Ramsay sedation scale was used for assessment of the parturients sedation: 1 = anxious or restless, 2 = cooperative and tranquil, 3 = respond to

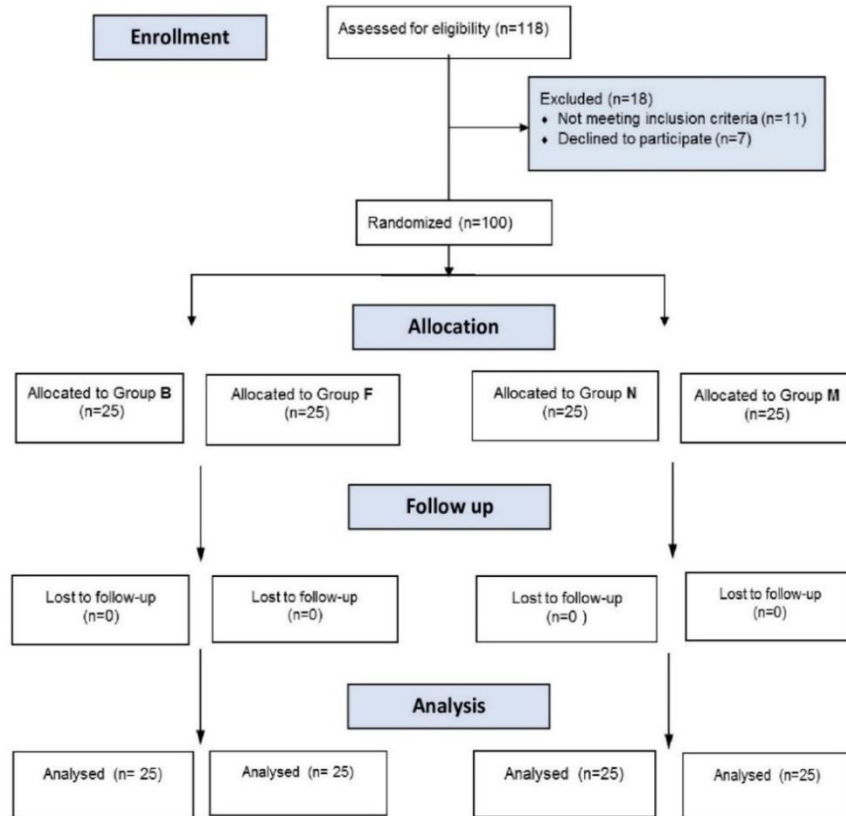


Figure 1: CONSORT flowchart

orders only, 4 = rapid reaction to raised voice or slight glabellar taps. 5 = Slow reaction to raised voice or slight glabellar taps. 6 = nil response to raised voice or glabellar tapping.

The delivered babies were examined and Apgar score noted at one and five minutes after birth by the pediatrician not involved in the study.

The duration of effective analgesia during the first 24 h postoperatively was set as the primary outcome. The secondary outcomes included the sensory and motor blockade characteristics (onset and duration), postoperative pain scores and pethidine requirements, the LA related complications, maternal sedation score, and neonatal Apgar scores.

According to a prior study⁶ and the hypothesis that midazolam would provide similar effect to fentanyl and nalbuphine when added to bupivacaine in spinal anesthesia and would increase the effective analgesia time in the first 24 h postoperatively by 30% when

Table 1: Demographic characteristics

Variable	Group B (n = 25)	Group F (n = 25)	Group N (n = 25)	Group M (n = 25)	P-value
Age (y)	29.68 ± 5.42	28.76 ± 4.44	26.52 ± 5.38	28.44 ± 5.08	0.172
Weight (kg)	72.48 ± 7.14	69.48 ± 7.05	71.40 ± 7.29	70.88 ± 6.21	0.493
Height (cm)	167.68 ± 5.15	166.88 ± 3.63	169.08 ± 4.13	168.76 ± 4.45	0.269
Duration of surgery (min)	57.48 ± 9.78	57.76 ± 11.29	56.80 ± 10.02	58.20 ± 13.11	0.976

Values are presented as mean ± SD

compared to control group. With α error of 0.05, power of 0.8, and an effect size of 0.36, a sample size of 23 parturients was required per group. To account for the possible dropouts, we included 25 parturients per group. The G Power 3.1.9.4 (Universitat Keil, Germany) software was employed for the sample size estimation.

3. Results

Subjects enrolled in the study were 118 parturient females. Eleven were excluded for not meeting the inclusion criteria and seven for not willing to participate. The remaining one hundred patients participated in the analysis (25 in each group), with no dropouts (Figure 1).

Table 2: Characteristics of sensorimotor blockade

Variable	Group B (n = 25)	Group F (n = 25)	Group N (n = 25)	Group M (n = 25)	P-value
Sensory onset (min)	3.14 ± 0.89	2.50 ± 0.78	2.43 ± 0.67	2.96 ± 0.79	0.003*
Motor onset (min)	5.51 ± 0.73	4.81 ± 0.86	4.83 ± 0.95	5.07 ± 0.88	0.017*
Time to 2-segment regression (min)	105.84 ± 17.11	119.64 ± 17.45	117.72 ± 13.56	118.01 ± 15.14	0.010*
Duration of sensory block (min)	134.24 ± 22.61	173.05 ± 18.99	162.22 ± 23.93	165.98 ± 25.17	< 0.001**
Duration of motor block (min)	134.23 ± 7.92	144.78 ± 11.50	141.46 ± 8.65	143.11 ± 7.65	< 0.001**

*Values are presented as mean ± SD; *Statistically significant (P < 0.05); **highly significant (P < 0.001).*

Statistical analysis

SPSS version 25 (IBM, Armonk, New York, United States) was used for statistically analyzing the measured data. Means ± standard deviations (SD) were employed to express quantitative data, while numbers and percentages were employed to express qualitative data. To compare between more than two groups of variables; the one-way (ANOVA) test was used for parametric data, and Kruskal-Wallis test for continuous non-parametric data, followed by the post hoc test if significant results were detected. Chi-squared test or Fisher exact test were used for comparison of qualitative variables between the groups. P < 0.05 was regarded as statistically significant (S), and P < 0.001 regarded as highly significant (HS).

Parturients demographic data, age, weight, height, and duration of surgery, were statistically comparable among the four groups (Table 1).

Onset of sensory and motor blocks was significantly earlier in Group-F and Group-N than Group-B. While Group-M didn't achieve any significant difference with other groups. Durations of sensory and motor blocks were significantly longer in F, N and M Groups than Group-B with insignificant intergroup differences between adjuvants. Duration of 2-segment regression was significantly longer in F, N and M Groups than Group-B with insignificant intergroup differences between the adjuvants (Table 2).

The duration of analgesia was significantly prolonged in F, N and M Groups as compared to Group-B, with

Table 3: Effective analgesia duration and consumed analgesic dose in the first 24 hours postoperative:

Variable	Group B (n = 25)	Group F (n = 25)	Group N (n = 25)	Group M (n = 25)	P-value
Duration of effective analgesia (min)	172.11 ± 20.99	252.42 ± 46.11	227.34 ± 36.54	243.71 ± 44.95	< 0.001**
Total pethidine dose (mg/24 h)	74.80 ± 27.56	39.80 ± 26.39	41.00 ± 33.32	40.20 ± 32.89	< 0.001**

*Values are presented as mean ± SD; *Statistically significant (P < 0.05); **highly significant (P < 0.001)*

Table 4: Neonatal outcome and maternal sedation score:

Variable	Group B (n = 25)	Group F (n = 25)	Group N (n = 25)	Group M (n = 25)	P-value
Apgar score at 1 min	7.48 ± 1.39	7.16 ± 1.57	7.64 ± 1.32	6.92 ± 1.26	0.264
Apgar score at 5 min	9.44 ± 0.71	9.24 ± 0.78	9.36 ± 0.76	8.96 ± 1.06	0.202
Sedation score	1.84 ± 0.62	2.40 ± 0.83	2.12 ± 0.73	2.80 ± 0.82	< 0.001**

Values are presented as mean ± SD. **highly significant (P < 0.001)

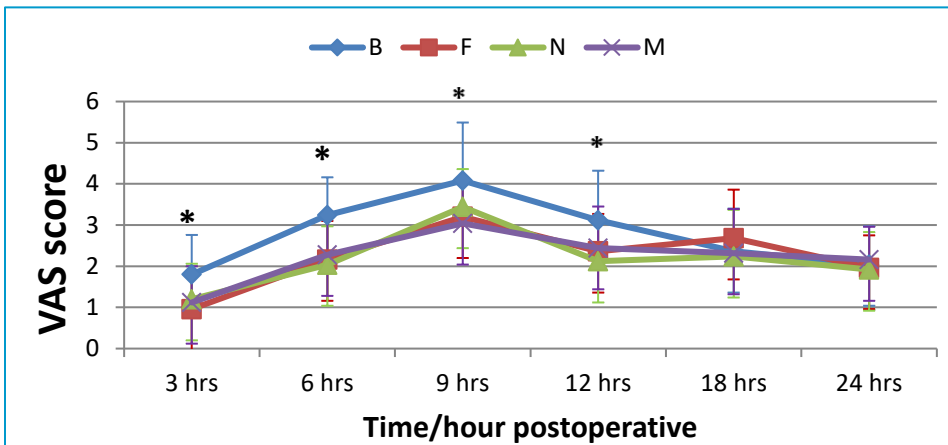


Figure 2: Comparison of postoperative VAS among studied groups. *Statistically significant (P < 0.05) **highly significant (P < 0.001)

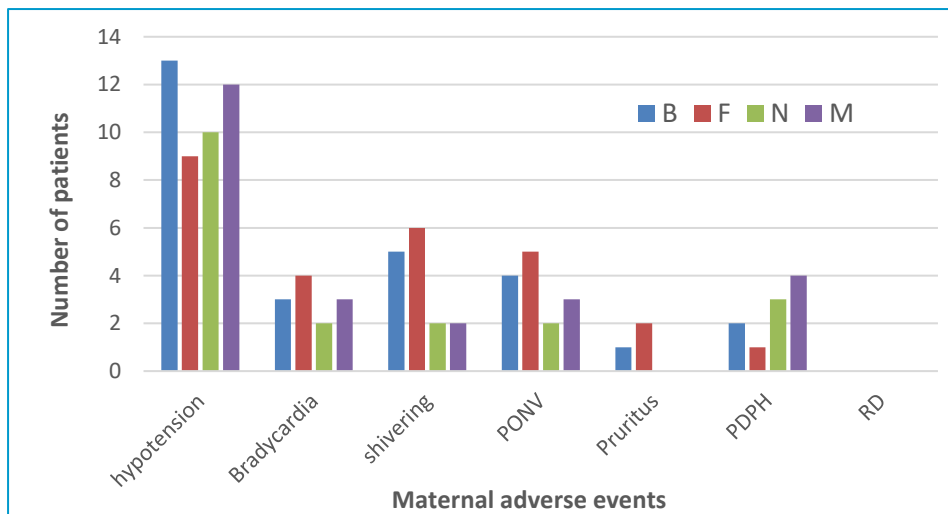


Figure 3: The maternal adverse events in the groups. PONV = postoperative nausea and vomiting; PDPH = post dural puncture headache; RD = respiratory distress

insignificant intergroup differences between the adjuvants. Also, a significant decrease in pethidine doses were required postoperatively in F, N and M Groups compared to Group-B with insignificant intergroup differences (Table 3).

subarachnoid block. Despite the increased number of cases of post-spinal shivering, PONV and pruritus in Group-F, but it couldn't reach a significant value compared to others (Figure 3).

Lower VAS scores were displayed in F, N and M Groups at 3 h up to 12 h postoperative than in Group-B. F and M Groups scored significant decrease at 3, 6 and 9 h compared to Group-B, and Group-N scored significant decrease at 6 and 12 h. No significant differences were observed later between the groups at 18 and 24 h postoperative (Figure 2).

Neonatal Apgar scores at 1 min and 5 min were comparable among the four groups. Sedation score was significantly higher in Group-F and Group-M than Group-B while Group-N didn't achieve any significant difference compared to Group-B (Table 4).

Insignificant differences were displayed among the groups as regard the maternal adverse events related to

4. Discussion

The clinical application of local anesthetics (LA) in the pain management field is restricted by its short duration of action and the dose dependent side-effects. Adjuvants or additives are frequently used with LA due to their synergistic action through intensifying the duration of sensorimotor block and attenuating its undesirable effects. Various drugs such as opioids, adrenalin, clonidine, magnesium sulfate, midazolam, neostigmine, ketamine, and steroids have been used to potentiate the effect of LA.⁷

We investigated the effectiveness of combining intrathecal LA with opioids (fentanyl and nalbuphine) versus a benzodiazepine (midazolam) versus placebo (saline). Three different mechanisms of action were employed: Fentanyl as a strong μ -opioid receptor agonist, nalbuphine as a mixed agonist-antagonist acting on μ - and kappa opioid receptors, and midazolam as GABA receptor agonist. Their influence on the hyperbaric bupivacaine characteristics were studied and recorded in cesarean sections.

Regarding the primary outcome, the current study results demonstrated a significant prolongation of analgesic action and less rescue analgesia requirements when additives were added to LA compared to bupivacaine alone. However, comparable intergroup differences were noted among the three additives. These outcomes agree with Yektas who studied the analgesic postoperative characteristics of seven different intrathecal adjuvant agents including fentanyl and midazolam; and didn't find significant differences in the time to first analgesic request among the adjuvants.⁸ Goma HM et al., also compared the postoperative analgesic properties of intrathecal fentanyl (25 μ g) with nalbuphine (0.8 mg) in sixty parturients who underwent elective CS under SA and didn't find any significant difference in the duration of analgesia between the two.⁹ Sabry et al., had also reported a non-significant difference between intrathecal nalbuphine and fentanyl regarding the time to first rescue analgesic requirement and the total amount of utilized diclofenac sodium following tibial fixation surgery.¹⁰

Another study by Bharti et al., comparing intrathecal midazolam (2 mg) and fentanyl (25 μ g) in endoscopic urological surgeries, proved that both offered similar advantages regarding duration of complete and effective analgesia postoperatively.¹¹ A similar comparison, performed by Elfawal et al., also confirmed the same results.¹²

Several studies reported similar outcomes regarding the superiority of the analgesic effect of LA when adjuvants were added, but with various intergroup differences. Some studies reported that intrathecal fentanyl had a superior analgesic action in comparison to nalbuphine or

midazolam.^{13,14} Other studies favored the use of intrathecal nalbuphine as it provided better postoperative analgesia and lower

+ adverse events than fentanyl or midazolam.¹⁵⁻¹⁷ Further studies informed better outcomes achieved by intrathecal midazolam over nalbuphine.^{18,19}

On the contrary, Sawhney et al., who studied the impact of combining fentanyl or midazolam with LA in lower limb operations versus bupivacaine alone, stated that adding adjuvants did not significantly extend the length of the block.²⁰ These dissimilar outcomes might be related to the lower dosage used (10 μ g fentanyl and 1 mg midazolam) compared to current study dosage. Furthermore, one study claimed that addition of adjuvants had caused reduction in duration of the block.²¹

As regard sensorimotor blockade characteristics, current study results demonstrated a quality improvement in SA when adjuvants were added to LA. Time to onset of sensory and motor blocks was shorter in adjuvant groups than controls with comparable differences between fentanyl and nalbuphine. However, the midazolam group showed comparable onset timing with controls. This could be explained by the increase in lipid solubility of fentanyl and nalbuphine; therefore, the tissue uptake was more than midazolam. These outcomes agree with Goma et al., who noted rapid comparable sensory and motor block onset timing achieved by both fentanyl and nalbuphine in CS.⁹ Meanwhile, Shadangi et al., reported that onsets of sensory and motor blocks were comparable between the controls and midazolam group.²²

Two segment regression from highest sensory level was slower in adjuvant groups than in controls with comparable intergroup differences among additives. These outcomes agree with Sabry et al. study which recorded insignificant differences between intrathecal fentanyl and nalbuphine regarding two segments regression time.¹⁰ Also, Bharti et al., noted that regression of the sensory level to S2 segment was significantly delayed in the fentanyl and midazolam groups in comparison to the bupivacaine alone with comparable intergroup differences.¹¹

Duration of sensory and motor blocks was prolonged in fentanyl, nalbuphine and midazolam groups in comparison to bupivacaine alone with insignificant intergroup differences among adjuvants. These outcomes agree with other researchers who demonstrated similar outcomes.⁹⁻¹¹

As regard postoperative VAS, current study results showed statistically significant differences in VAS scores among the four groups from the 3rd to the 12th postoperative hours, followed by comparable scores

among the groups in the remaining 24 h. These outcomes agree with Fawaz et al. and AL-Morsy et al. studies which revealed better pain scores in the early postoperative period when adjuvants were used.^{14,15}

The incidence of maternal adverse effects couldn't achieve significant differences among the four groups. Although, fentanyl group was associated with more cases of post-spinal shivering, PONV and pruritus, but the differences were insignificant. These outcomes agree with earlier studies.^{9,19,23}

As regard maternal sedation score, current study demonstrated significant differences among the groups with lowest score in Group-B and highest score in Group-M. The results agree with Amin et al. who recorded scores of $(0.61 \pm 0.32$ vs $2.75 \pm 0.54)$ in controls and midazolam respectively, ($P < 0.001$).⁴ Also, Thakkar et al. found more sedative effect of intrathecal midazolam than nalbuphine,¹⁸ but others did not.^{12,19,22}

Apgar scores at 1 min and 5 min after childbirth demonstrated no significant differences among the four groups. There weren't any reported cases of neonatal morbidity or mortality. These outcomes agree with Ahmed's study, comparing the effect of intrathecal fentanyl and nalbuphine; which reported that neonatal Apgar scores were comparable in both groups.²³ Kapdi et al. also observed that adding intrathecal midazolam to bupivacaine had extended the postoperative analgesia without causing harm to baby or mother.¹⁹ In contrast, Amin et al., observed a lower Apgar score at 1 min in midazolam group than in nalbuphine and control groups.⁴

5. Limitations

Some limitations were observed in the study; initially, analysis of different drug-doses wasn't performed and so, the adjuvant doses which produce minimal and maximal adverse effects couldn't be determined. Also, the study was restricted to females who didn't complain of any comorbidity like diabetes or hypertension. Finally, different obstetricians had performed the CS and the lengths of cutaneous incision weren't considered, which might affect the pain-related outcomes. Further trials could be performed to overcome such deficits.

6. Conclusion

Improved outcomes had accompanied the addition of adjuvants to intrathecal bupivacaine in elective CS. The sensory and motor blockade were earlier in onset, longer in duration, with prolonged postoperative analgesia and less opioid consumption. Intrathecal midazolam revealed respectable outcomes in terms of

improving anesthetic and analgesic properties of LA, with low rates of adverse events.

7. Conflict of Interest

The authors declared no potential conflict of interest relevant to this article.

8. Trial registration

The study was registered at the clinicaltrials.gov with special number (NCT04932083).

9. Conflict of interest

No conflict of interest is declared by the authors.

10. Data availability

The numerical data related to the study is available with the corresponding author.

11. Author contribution

SR: study design, data collection, analysis and interpretation, and writing the manuscript.

IS: literature search, data collection and editing of the manuscript.

EA: conception and design of the study, literature search, and critical revision of the article for important intellectual content. All authors have read, revised, and approved the final manuscript.

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