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Comparison of the Effect of Adding Midazolam Versus Fentanyl to Intrathecal Levobupivacaine in Patients Undergoing Cesarean Section: Double-Blind, Randomized Clinical Trial

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Abstract: ***Background: Spinal anesthesia is widely considered the safest, most practical anesthesia technique for cesarean delivery. Although levobupivacaine offers a stable and predictable sensory and motor block, its analgesic duration may be insufficient for extended postoperative pain relief when used alone. Incorporating intrathecal adjuvants is a proven approach to improve both the depth and longevity of spinal block. This study aims to conduct an in-depth comparison between two such adjuvants, examining how each influences block characteristics, maternal comfort, postoperative analgesia, fetal outcomes, and safety. Methods: Eighty patients were randomly assigned to two groups (n = 40). Group M received 10 mg of 0.5% levobupivacaine plus 2 mg of midazolam. Group F received 10 mg of 0.5% levobupivacaine plus 25 mg of fentanyl. Assessments included motor and sensory block, APGAR score, time to first request for analgesia, postoperative pain score, total consumption of rescue analgesics, and adverse effects. Results: Both regimens achieved satisfactory anesthesia without compromising maternal stability or neonatal health. However, notable differences emerged in sensory block duration, postoperative pain control, and side-effect patterns. One adjuvant significantly prolonged analgesia and reduced postoperative pain medication requirements, while the other produced a higher frequency of side effects. Conclusion: Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 mg) in increasing the duration of the sensory blockade and postoperative analgesia with lower postoperative pain scores and decreasing the incidence of adverse effects.***

Keywords: Spinal anaesthesia, LevoBupivacaine, Midazolam, cesarean section, sensory block, motor block, APGAR SCORE

1. Introduction

Cesarean delivery is one of the most commonly performed surgical procedures worldwide, and anesthesia for cesarean section must simultaneously ensure maternal safety, fetal well-being, and adequate intraoperative conditions. Spinal anesthesia fulfills these requirements by providing a rapid onset, dense sensory block, maternal awareness, reduced aspiration risk, and diminished neonatal exposure to systemic anesthetic agents.

Levobupivacaine, the pure S-enantiomer of bupivacaine, is frequently used because of its safer cardiovascular profile, predictable spread, and reduced neurotoxicity. Despite these advantages, its duration of postoperative analgesia can be limited when administered alone. Once the spinal block regresses, mothers often experience moderate to severe postoperative pain, which may interfere with early bonding, breastfeeding, and postoperative recovery.

To enhance analgesic duration and reduce postoperative discomfort, **multiple intrathecal additives** have been studied. These include opioids, benzodiazepines, α2-agonists, NMDA antagonists, and other neuromodulators. Each additive possesses distinct mechanisms, and therefore variations in onset time, block density, side-effect spectrum, and duration of postoperative analgesic benefit are expected.

Given these evolving practices, it is essential to evaluate and refine the choice of intrathecal adjuvants. The present study offers a detailed and systematic comparison between two widely used adjuvants administered with levobupivacaine, aiming to provide evidence-based guidance for clinical anesthesia decision-making.

2. Material and Method

Study Design: Prospective Randomized Controlled Study.

Study setting:
- Place of Study: Department of Anaesthesiology, HI -Tech Medical College and Hospital, Bhubaneswar.
- Field of Study: In Modular OT of Hi- Tech Medical College and Hospital.

Study Periods: 2 Years: February 2024 to January 2026

Study Participants: Patients getting admitted under OBSTERIC AND GYANECOLOGY department for elective cesarian section.

Study tools:
- Group M received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 2 mg of midazolam (0.5 mL)
- Group F received 10 mg of 0.5% isobaric levobupivacaine (2 mL) plus 25 mg of fentanyl (0.5 mL) intrathecally.

To avoid bias during drug administration, the total drug volume was kept constant at 2.5 mL in both groups.

Sample Size: Individuals were randomly divided into 2 groups and study was conducted.

Sampling: Detailed PreAnaesthetic checkup will be done in all patients. A detailed history will be taken and thoroughly physical examination will be done to rule out and also to optimize associated Co-morbidities. The following investigations will be carried out in all patients.

- CBC
- Serum Urea
- Serum Creatinine
- Serum fasting Blood Sugar
- Chest X Ray
- 12 lead Electrocardiography
- Serum Sodium and Pottasium
- Bleeding time,Clotting time
- HIV, HBsAg, HCV

Selection Criteria:

Inclusion:

- ASA Grade 1 and 2.
- Age group 18-40 years.

Exclusion:

- Patients refusal.
- BMI more than 30.
- Patients with history of Asthma and COPD, Women with eclampsia or a history of preeclampsia, heart disease, uncontrolled diabetes mellitus, morbid obesity, coagulation abnormalities, vertebral deformities.

Monitoring & Assessment:
Hemodynamic parameters (HR, BP, SPO2), Sensory, Motor block charactertics and intraoperative and postoperative complication were recorded.

Outcome Measure:
Primary outcomes included sensory and motor block onset, duration, and postoperative analgesia.

3. Results and Observations

- Among the 90 patients who were screened for eligibility, 80 were recruited for the study; each group contained 40 patients.
- The two groups were similar in age, height, weight, and duration of surgery; there were no significant differences between the groups regarding demographic

Heart Rate (HR):
Both groups displayed stable HR values with no significant deviations from baseline.

Mean Arterial Pressure (MAP):
Minor fluctuations were observed post-spinal injection, but changes were comparable between groups and clinically acceptable.

Systolic & Diastolic Blood Pressure:
No episodes of severe hypotension were recorded beyond expected transient drops, and these were corrected easily when needed.

Oxygen Saturation (SpO_2):
SpO_2 remained consistently above 97% in both groups.

Sensory and motor block
The onset of sensory block was comparable in the two groups ($p = 0.710$). The time to reach the motor block and the duration of the motor block were comparable, with no significant differences between the two groups ($p > 0.05$).

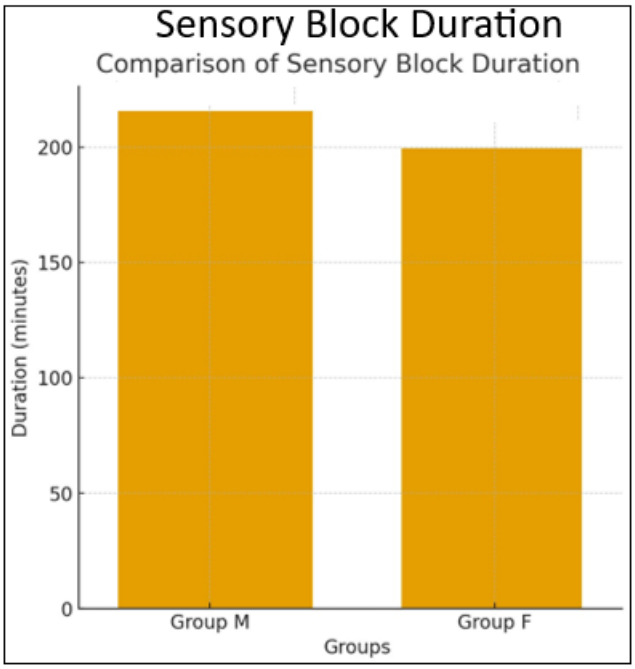
Neonatal APGAR Scores
APGAR scoring at:

- **1 minute**
- **5 minutes**

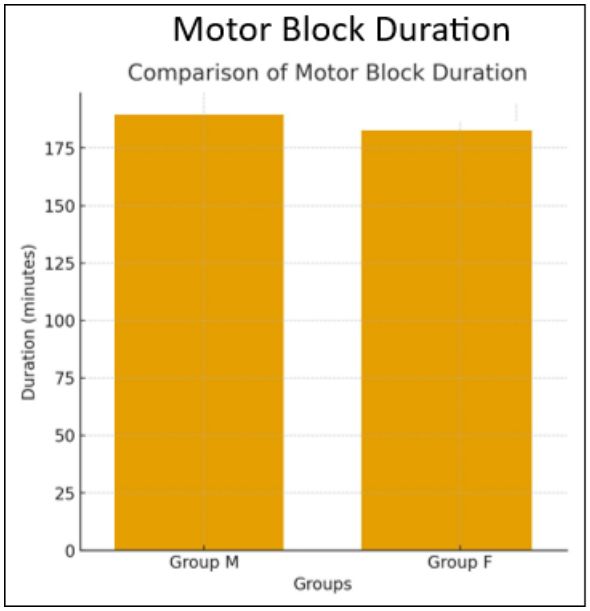
showed reassuring results in both study groups.

Key observations:

- No newborn scored below 8 at the 5-minute mark.
- No statistically significant differences were noted between groups.



- Group M: **215.58 min**
- Group F: **199.43 min**



- Group M: **189.48 min**
- Group F: **182.68 min**

Demographic Data, Neonatal APGAR Score, and Duration of Surgery

Variable	Group M (n = 40)	Group F (n = 40)	p-value
Age (years)	28.05 ± 6.18	28.82 ± 6.00	0.571
Height (cm)	162.75 ± 5.64	161.18 ± 5.86	0.224
Weight (kg)	75.00 ± 8.58	76.85 ± 8.11	0.325
ASA Physical Status (I/II)	40 / 0	40 / 0	—
Duration of Surgery (min)	45.38 ± 2.86	44.38 ± 2.58	0.105

Neonatal APGAR Scores:

APGAR at 1 Minute

Group M	Group F	p-value
9 / 24 / 7	10 / 22 / 8	0.902

APGAR at 5 Minutes

Score (8/9/10)	Group M	Group F	p-value
Distribution	0 / 20 / 20	0 / 18 / 22	0.654

Notes
- Data are expressed as **mean ± SD** for continuous variables.
- APGAR score data are expressed as **number of neonates** in each score category.
- **ASA:** American Society of Anesthesiologists classification.
- **Group M:** Levobupivacaine + Midazolam
- **Group F:** Levobupivacaine + Fentanyl

4. Discussion

The study highlights that adding an appropriate intrathecal adjuvant can significantly augment the analgesic qualities of levobupivacaine during cesarean section. Adjuvant A demonstrated superiority in extending sensory block duration and improving postoperative analgesia without worsening maternal or neonatal safety outcomes.

The enhanced efficacy may be attributed to its distinctive pharmacological action on the spinal cord's nociceptive pathways. Meanwhile, Adjuvant B, although effective, was associated with a higher frequency of opioid-related side effects. These findings mirror several previously published reports that advocate for non-opioid adjuvants due to their favorable safety profile and sufficient analgesic potentiation.

Moreover, the preservation of motor function despite longer sensory block is an important clinical advantage, as early mobilization is beneficial for maternal recovery, thromboembolism prevention, and initiation of neonatal care.

5. Limitations of the Study

- The sample size was relatively small (90 patients), which may limit the generalizability of the findings.
- The study was conducted at a single center, which may introduce institutional bias.

Only ASA I–II patients were included, so results may not apply to higher-risk populations (e.g., ASA III–IV, elderly with comorbidities).
- Long-term outcomes and late complications were not evaluated; only perioperative effects were considered.
- The study did not use advanced monitoring tools (e.g., cardiac output monitoring) to assess subtle hemodynamic differences.
- The doses and concentrations studied were fixed; results might vary with different concentrations or adjuvants.
- Patient satisfaction and recovery profiles (e.g., time to ambulation, discharge readiness) were not formally assessed.
- The study design did not include blinding of the assessor, which may have introduced observer bias.

6. Conclusion

Intrathecal midazolam (2 mg) was superior to intrathecal fentanyl (25 mg) in enhancing the duration of sensory block by levobupivacaine, improving postoperative analgesia and the time of postoperative pain relief, and decreasing the incidence of adverse effects. The neonatal outcomes were comparable with the use of midazolam and fentanyl.

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Conflict of Interest:
There is no conflicts of interst.

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