

ORIGINAL RESEARCH

REGIONAL ANESTHESIA

Intrathecal bupivacaine with fentanyl compared to levobupivacaine with fentanyl for painless labor: a double-blind, randomized clinical trial

Wesam Nashat Ali¹, Hamdy Abbas Youssef², Ahmed Mohammed Abbas³, Peter Eleshah Roshdy⁴, Ahmed Said Saad Imbaby⁵

Authors affiliation:

1. **Wesam Nashat Ali**, Assistant Professor in Anesthesia and intensive care department, faculty of medicine, Assiut University, Assiut, Egypt. E-mail address: wesamnashat@aun.edu.eg
2. **Hamdy Abbas Youssef**, Professor in Anesthesia and intensive care department, faculty of medicine, Assiut University, Assiut, Egypt. E-mail address: hamdy.badawi@med.aun.edu.eg
3. **Ahmed Mohammed Abbas**, Assistant Professor in gynecology and obstetrics department, faculty of medicine, Assiut University, Assiut, Egypt. E-mail address: ahmedabbas@aun.edu.eg
4. **Peter Eleshah Roshdy**, Resident in Anesthesia and intensive care department, faculty of medicine, Assiut University, Assiut, Egypt. E-mail: drpetersh3sh3@gmail.com
5. **Ahmed Said Saad Imbaby**, Lecturer in Anesthesia and intensive care department, faculty of medicine, Assiut University, Assiut, Egypt. E-mail address: snakah3@aun.edu.eg

Correspondence: Marwa Mahmoud Abdelrady; Fax: +2 088 2333327; Phone: +201005802086; E-mail: marwarady@med.aun.edu.eg

ABSTRACT

Background & Objective: Labor pain relief has been a challenge for the clinicians for centuries. A lot many regimes and therapeutic interventions, including spinal and epidural injections, have been tried with variable effect. We aimed to compare the duration of analgesia and potency of bupivacaine plus fentanyl vs. levobupivacaine plus fentanyl for painless labor.

Methodology: We enrolled 70 parturients who requested spinal analgesia in active labor, and randomly divided them into two groups; Group B (35 women) received 2.5 ml of bupivacaine 0.5% plus fentanyl 25 µg, and Group L (35 women) received 2.5 ml of levobupivacaine 0.5% plus fentanyl 25 µg. We assessed motor and sensory block, the efficacy of analgesia, pain scores, adverse effects, and obstetric and neonatal outcomes of both groups.

Results: Time to reach maximum sensory block was significantly longer in Group L than in Group B ($P = 0.002^*$). There was a statistically significant increase in the duration of motor blocks in Group B than in Group L ($P < 0.05$). The median VAS scores were significantly lower in Group L than in Group B after 2 and 3 h after injection. The duration of analgesia was significantly longer in Group L than in Group B ($P < 0.05$). The two study groups had no differences in the measured obstetric and neonatal outcomes.

Conclusion: Levobupivacaine with fentanyl was superior to bupivacaine with fentanyl regarding the duration and potency of analgesia with lower pain scores, high maternal satisfaction, and no adverse obstetric or neonatal outcomes. Therefore, spinal levobupivacaine plus fentanyl was a reasonable choice for labor analgesia and can be used without jeopardizing the safety of the mother and fetus.

Key words: Bupivacaine; Fentanyl; Levobupivacaine; Labor pain; Spinal Analgesia

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1. INTRODUCTION

Childbirth is the most painful experience a woman can have in her lifetime. Dilation of the lower uterine segment and cervix causes pain in the early stages of labor; the descent of the fetus in the birth canal causes distension and tearing of tissues in the vagina and perineum, resulting in pain in the late first and second stages of labor.¹

Labor pain increases catecholamine release and constricts blood vessels, so it can be dangerous to both the mother and the baby. Pain might also cause maternal discomfort; hyperventilation causes hypocapnia, enhances uterine vascular constriction, and decreases the mother's ventilatory drive between contractions. As a result, the oxygen dissociation curve of the mother shifts to the left. These components put the fetus's oxygen supply in danger, possibly resulting in fetal hypoxia and fetal metabolic acidosis.²

The gold standard in labor analgesia is epidural services. They are widely used to provide pain-free labor in many regions of the world and enable flexibility to match each patient's needs.³ Epidurals have long been linked to increased oxytocin use, fetal malposition, instrumental and cesarean birth, and prolonged labor.⁴

Single-shot intrathecal low dosage injections are beneficial.⁵ The benefits of this approach include rapid onset and consistency, and minimal hemodynamic alterations and motor block. A spinal block is less expensive and technically less complex than epidural and combination spinal-epidural blocks. When the duration of labor can be accurately approximated, intrathecal analgesia alone can be helpful. Rapid analgesia is provided by combining an opioid with a modest dosage of local anesthetic. Bupivacaine has been a popular alternative for labor analgesia due to its low placental transfer, strong protein binding, and less motor block than the sensory block in lower dosages. The addition of neuraxial lipid-soluble opioids allowed the dose to be reduced while maintaining adequate analgesia and eliminating potential side effects such as labor progression and lower extremity motor block.¹

Levobupivacaine, the pure S (-) enantiomer of bupivacaine, has emerged as a far safer alternative to its racemic brother, bupivacaine, for regional anesthetic. Levobupivacaine has been discovered to have the same efficacy as bupivacaine but with a better pharmacokinetic profile.⁶

We aimed to assess the analgesic duration and potency of intrathecal injection of bupivacaine and fentanyl versus levobupivacaine and fentanyl for normal vaginal delivery analgesia.

2. METHODOLOGY

The Medical Ethics Committee (IRB no 17100898), Faculty of Medicine, Assiut University, Egypt, approved this prospective, double-blind, randomized, controlled study, conducted in Assiut University Women's Health and prospectively registered in the clinicaltrials.gov registry (Identifier: NCT04221568). All parturients signed written and verbal informed consent forms. This research began in June 2020 and was completed by June 2021.

This study included 70 females over 18 y of age, at term pregnancy, ASA class II, parturients with singleton pregnancies, vertex presentation, and parturients in active phase of labor with a cervical dilatation > 4 cm.

The exclusion criteria included women with eclampsia or a history of preeclampsia, heart disease, uncontrolled diabetes mellitus, labor dystocia, abnormal or indeterminate fetal heart rate tracing, fetal malpresentation, multiple gestations, refusal of the parturients, and suspected fetal macrosomia, a fetus with known or suspected congenital abnormalities, administration of parenteral or oral analgesics before initiation of neuraxial analgesia.

Using a computer-generated database of random numbers, the parturients were divided into two groups; Group B: 35 parturients received an intrathecal injection of 0.5% hyperbaric bupivacaine 10 mg (2 ml) and fentanyl 25 µg (0.5 ml) and Group L: 35 parturients received an intrathecal injection of 0.5% hyperbaric levobupivacaine 10 mg (2 ml) and fentanyl 25 µg (0.5 ml).

In both of the groups we kept the total drug volume constant to avoid bias during drug delivery.

The drug syringes were prepared by investigators who were not involved in the data collection. The intervention assignments were unknown to the surgeon, the parturients, the anesthesiologist, and the investigators who gathered the data and assessed the outcomes. The syringe codes were kept in envelopes ranging from 1 to 70. Only one anesthesiologist who packed the envelopes had access to the codes.

Intrathecal analgesia procedure

On the nondominant hand, an intravenous line was established with an 18 G cannula, and the parturients were preloaded with 500 ml of ringer's lactate solution. The blocks were performed in a sitting position with a 25 G spinal needle at L3-L4 interspace. Participants received a single intrathecal injection of the previously stated solutions after the return of clear cerebrospinal fluid. They were then shifted to a supine position with left lateral displacement.

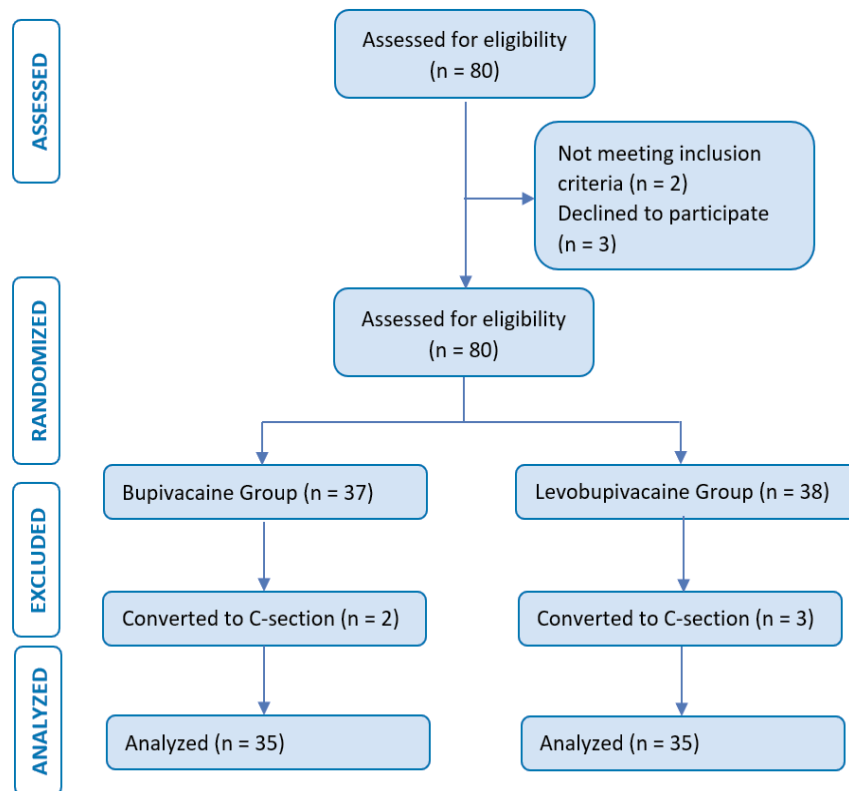


Figure 1: CONSORT flow diagram

Maternal blood pressure and heart rate were measured noninvasively at the start and at 1 min, and then every 5 min till 30 min, and then every 15 min till the delivery. Maternal hypotension was defined as a systolic arterial pressure of 90 mmHg or 20% lower than the baseline and was treated by increasing the intravenous infusion rate and, if necessary, intravenous ephedrine.

The onset of analgesia was evaluated as the time of injection until the first painless contraction occurred. The effectiveness of the block was evaluated using a visual analog scale (VAS). The sensory loss to pinprick was assessed bilaterally at each dermatomal level. The time gap between drug delivery and maximum pinprick score was used to determine the beginning of the sensory blockade.

Motor block was evaluated using a modified Bromage scale by evaluating the ability to raise a leg for 30 sec. The time interval between the spinal and a modified Bromage score of 3 was used to determine the beginning of the motor blockade.

Cardiotocography (CTG) was used to monitor fetal wellbeing and uterine contractions. A 30-min post-injection time was taken into account when comparing

uterine activity. The length of the first and second stages of labor and the delivery technique were all documented. Apgar scores at 1 and 5 min were used to determine neonatal wellbeing.

Adverse effects from the spinal block, such as itching, hypotension, nausea, and vomiting, were documented and compared in the two groups after each spinal injection.

Patient satisfaction score (Likert scale) was established by asking parturients about their experiences with anesthesia during the intraoperative and postoperative periods. It was categorized as follows: (5–Extremely satisfied, 4–Satisfied, 3–Neutral, 2–Dissatisfied, 1–Extremely dissatisfied).

Another anesthesiologist in the PACU who was unaware of the drug used performed the postoperative assessment. The nurse in the ward responsible for the patient was also unaware of the drug used.

The duration of analgesia was the primary outcome. The time it took to obtain adequate motor and sensory block, the total length of the motor and sensory block, pain scores, the incidence of intraoperative hemodynamic alterations, the period of effective analgesia, and side effects such as pruritus, hypotension, nausea, and vomiting were all secondary outcomes.

Statistical analysis

Using the G-Power calculator 3.1.9.7 for sample size determination, a total sample size of 34 parturients in each group was determined to be sufficient for statistical testing based on a priori analysis with *t*-tests. Means: Difference between two independent means (two groups) with a two-tailed type I error of 0.05, a power of 0.8, and an effect size of 0.7.

The Shapiro-Wilk test the baseline variable distribution. Student's *t*-test and one-way analysis of variance with post hoc multiple was used to evaluate comparisons were used to assess continuous variables described as mean \pm SD). The Mann-Whitney U test was used to evaluate nonparametric data reported as median (range). The chi-square or Fisher's exact test examined categorical data reported as numbers and percentages. Statistical

Table 1: Comparison between both demographic and maternal data groups.

Parameter	Group B (n = 35)	Group L (n = 35)	P-value
Age (y)	31.49 ± 5.14	33.31 ± 4.98	0.135
Height (cm)	160.43 ± 5.65	158.57 ± 5.62	0.172
Weight (Kg)	86.69 ± 11.33	87.49 ± 9.83	0.753
Gestational age (Week)	38.11 ± 1.28	38.23 ± 1.21	0.703
Parity	2.80 ± 1.16	3.09 ± 1.09	0.239
Cervical dilatation (cm)	4.69 ± 1.05	4.77 ± 1.17	0.714
Intact membrane	26(74.3)	25(71.4)	0.788
Oxytocin use	15(42.9)	16(45.7)	0.810

Data presented as mean ± SD and number or percent; P < 0.05 considered as significant.

Table 2: Characteristics of the motor and sensory blocks, duration of analgesia, and 1st stage of labor.

Variable	Group B (n = 35)	Group L (n = 35)	P-value
Time to reach max motor block (min)	3.07 ± 1.09	2.60 ± 0.91	0.059
Time to reach max sensory block (min)	2.92 ± 1.06	2.20 ± 0.71	0.002*
Duration of motor block (min)	131.46 ± 41.71	99.11 ± 23.07	0.000*
Duration of analgesia (min)	119.11 ± 23.07	151.46 ± 41.71	0.000*
Duration of the first stage of labor (min)	106.43 ± 14.48	125.29 ± 24.70	0.000*

Data presented as mean ± SD; P < 0.05 considered as significant.

significance was defined as a $P < 0.05$. IBM SPSS statistics version 20 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

3. RESULTS

Out of 80 parturients screened for eligibility, 70 were recruited for the study; each group contained 35 parturients (Figure 1).

Demographic data including age, height, weight, gestational age, and parity were comparable in both groups with no significant differences ($P > 0.05$) (Table 1). There was no significant difference between the two groups as regards cervical dilatation, the status of the membrane, and oxytocin use ($P > 0.05$) (Table 1).

Hemodynamics: At any studied time, no significant differences were recorded between the groups in mean MAP, mean heart rate, or SpO₂. NIBP and HR were stable during the procedure (data not presented).

Sensory and motor block: Time to reach max sensory block (min) was significantly longer in Group L than in

Group B ($P = 0.002^*$). The time to reach the max motor block was comparable, with no significant differences between the two groups ($P > 0.05$). The duration of motor block in Group B was (131.46 ± 41.71 min), while in Group L was (99.11 ± 23.07 min); there was a statistically significant increase in the duration of motor block in Group B than in Group L ($P < 0.05$) (Table 2).

Pain relief profile: The median VAS scores were significantly lower in Group L than in Group B after 2 and 3 hours after injection, with no significant differences between the groups at other studied time points (Figure 2).

The duration of analgesia was significantly longer in Group L (151.46 ± 41.71 min) than in Group B (119.11 ± 23.07 min) ($P < 0.05$) (Table 2).

The duration of the first stage of labor was significantly longer in Group L (125.29 ± 24.70 min) than in Group B (106.43 ± 14.48 min) ($P < 0.05$) (Table 2).

Side effects: There were no significant differences between the two groups in the side effects. None of the

Table 3: Comparison between both groups in fetal monitoring and type of delivery

Fetal monitoring	Group B (n = 35)	Group L (n = 35)	P-value
Fetal bradycardia:	3 (8.60)	1 (2.9)	
APGAR:			
1 min 7/8/9	2/19/14	0/23/12	0.282
5 min 9/10	17/18	17/18	1.00
Delivery:			
Spontaneous	24 (68.6)	23 (65.7)	0.799
Instrumental	11 (31.4)	12 (34.3)	

Data presented as numbers and percentages; P < 0.05 considered as significant.

parturients complained of any neurologic deficits (Figure 3).

Patients' satisfaction: assessed by the Likert scale was adequate (very satisfied, satisfied, or neutral) in 94% of Group L and 80% of Group B parturients, with a significant difference between the groups (P = 0.012).

Fetal monitoring showed that only three fetuses had transient bradycardia, reversed spontaneously, in Group B and one in Group L. There was no significant difference between the two groups regarding fetal bradycardia, APGAR score 1min, 5min, and instrumental delivery (Table 3).

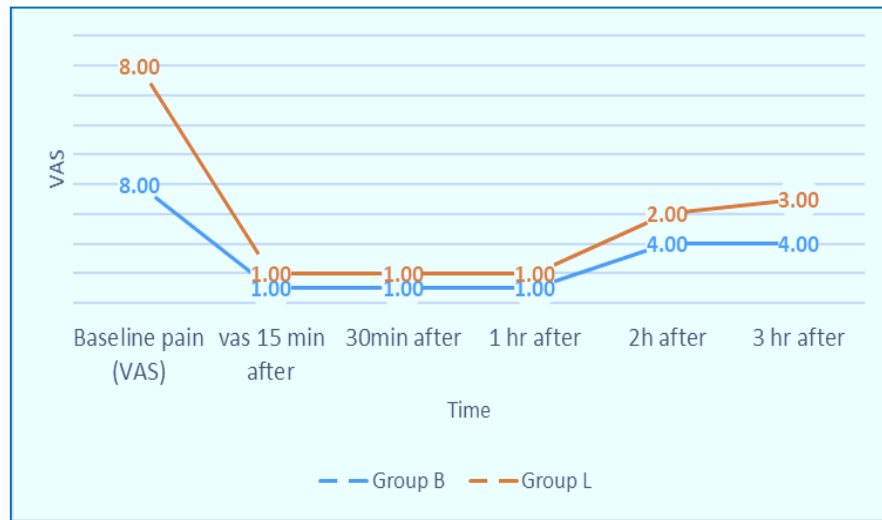


Figure 2: Comparative VAS scores in the two study groups

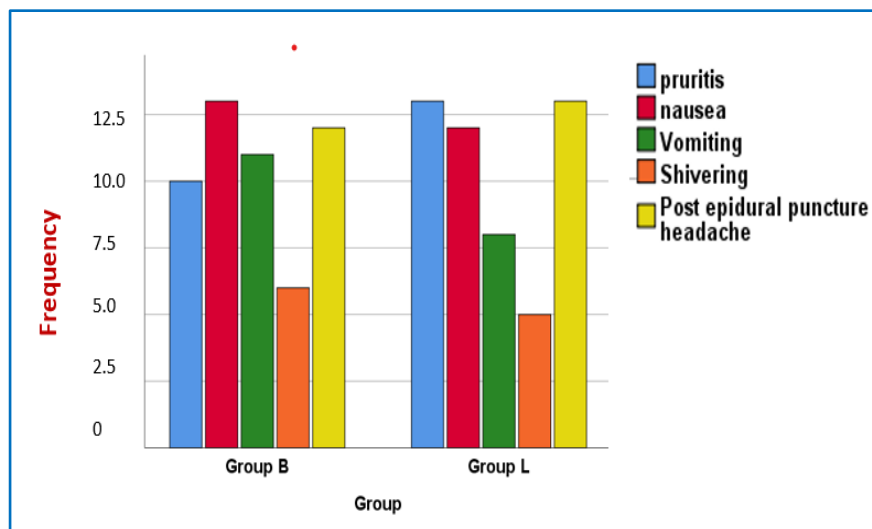


Figure 3: Comparison between both groups in adverse effects.

4. DISCUSSION

The fetus passes through the uterus and narrow vagina during vaginal delivery. Paroxysmal contractions and friction from the fetus' movement stimulate the mother's nerve endings and produce nerve impulses that pass from the lumbar plexus to the brain, causing severe pain during the delivery process.⁷ The mother not only experiences pain during delivery, but she also experiences unpleasant feelings such as anxiety and dread. These factors affect the success rate of vaginal deliveries.⁸

According to the findings of this study, the group receiving levobupivacaine plus fentanyl experienced analgesia faster than the group receiving bupivacaine plus fentanyl, with fewer side effects for the mother and a lower cesarean section rate. The quality of bupivacaine and levobupivacaine was equal; however, levobupivacaine had a longer duration of analgesia and less motor impairment than bupivacaine.

Single-shot spinal analgesia is one of the easiest techniques, with a success rate of 98% in parturients with severe restlessness due to pain during the later stages of labor, especially in resource-limited situations. One injection of a low-dose combination (fentanyl 25 µg, bupivacaine 2.5 mg, and morphine 250 µg) provides up to 4 h of ambulatory pain control.⁹

The addition of intrathecal opioids improves the efficacy of neuraxial local anesthetics. Anesthesia and analgesia are usually improved with such combinations. It also permits low local anesthetic dosages, resulting in more stable hemodynamics.¹⁰ Levobupivacaine and hyperbaric bupivacaine mixed with fentanyl generated a similar grade of sensory blocking and mother hemodynamic and neonatal consequences.

The parturients who had levobupivacaine and fentanyl had lower pain scores than those who had both bupivacaine and fentanyl. Fentanyl, lipophilic and a µ-receptor agonist, exerts its effect intrathecally by combining with opioid receptors in the dorsal horn of the spinal cord, which could have a supraspinal spread and action.

In addition to providing pain relief, neuraxial analgesia can cause motor blockade, which can lead to the inability to bear down by the mother. The use of low-dose local anesthetics these days for labor analgesia has significantly reduced the incidence of the motor blockade.¹¹ None of the parturients had motor impairment before the anesthetic procedure. The impairment of such motor function can result in higher instrumental delivery and cesarean section rates. The motor block observed in the current study had regressed completely before the commencement of the second stage of labor. Probably this explains why the maternal expulsive effort was also preserved.

Levobupivacaine is less likely to cause motor weakness than racemic bupivacaine. Motor impairment can alter the quality of bearing down and relaxing the pelvic muscles, resulting in dystocia and incorrect fetal head descent. Although this may increase the likelihood of instrumental and cesarean delivery,¹² the motor block changes did not affect the obstetric outcome. In the current study, the parturients were asked to rate their capacity to squeeze their perineal muscles. Although this is an unvalidated measure, we discovered that squeezing was subjectively hindered in more parturients.

Differences in the incidence of side effects and complications between the two groups did not reach statistical significance ($P > 0.05$). Hypotension in both groups responded to intravenous fluid administration. Intravenous ephedrine was not required in any patient. Nausea and vomiting occurred in both groups. These

parturients were given an injection of ondansetron 4 mg intravenously.

The present study showed that painless delivery does not adversely affect the neonates, so the average Apgar coefficient between the two groups in the first and fifth minute was approximately 9 and higher. The fetal heart rate (FHR) was also normal, and bradycardia occurred only in 4 neonates in both groups and reversed spontaneously. Moreover, there was no effect on the maternal side, and the hemodynamic changes were within the normal range.

5. LIMITATIONS

There are some limitations to this study. First, cord blood pH offers an objective retroactive marker of fetal hypoxia exposure and response during childbirth. Due to technical difficulties, we could not do so in our setup. Second, the results of our study could have been more precise if the study group's sample size had been larger; however, the number of parturients willing to receive labor analgesia in our hospital was limited.

6. CONCLUSION

Intrathecal levobupivacaine with fentanyl was superior to bupivacaine with fentanyl in terms of early-onset and longer duration of analgesia, with no detrimental effects on mothers and neonates. The combination of levobupivacaine and fentanyl also reduces motor block time, lowers the likelihood of side effects such as hypotension, and bradycardia, improves hemodynamic stability, and allows early mobility.

7. Data availability

Data generated during this study is available with the corresponding author.

8. Acknowledgments

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9. Conflict of interest

There are no conflicts of interest declared by the authors. This study was not funded by any government, private, or non-profit funding bodies.

10. Authors' contribution

All authors took part in the concept, conduct of the study, literature search and review, data recording and analysis and the manuscript preparation. All authors have approved the final manuscript.

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