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Original Research Article

Comparison Between Neostigmine and Fentanyl as Adjuvant to Bupivacaine in Epidural Labour Analgesia: A Randomized Control Trial

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Abstract

Background: Epidural analgesia is considered the gold standard for labour pain management. Opioid adjuvants such as fentanyl are commonly combined with bupivacaine to enhance analgesic efficacy and reduce local anesthetic requirement; however, opioid-related side effects remain a concern. Neostigmine, a cholinesterase inhibitor, has emerged as a potential non-opioid alternative for neuraxial analgesia.

Objective: To compare the analgesic efficacy and safety of neostigmine versus fentanyl as adjuvants to bupivacaine in epidural labour analgesia.

Methods: In this prospective randomized single-blinded controlled trial, 60 ASA I–II parturients in active labour were randomly allocated into two groups (n=30 each). Group N received epidural bupivacaine (1.25 mg/mL) with neostigmine 2 µg/mL, while Group F received bupivacaine with fentanyl 2 µg/mL. Primary outcomes included duration of analgesia and total bupivacaine consumption. Secondary outcomes included time to full cervical dilatation, rescue bolus requirement, maternal side effects, and neonatal outcomes. Statistical analysis was performed using appropriate parametric and non-parametric tests, with $p<0.05$ considered significant.

Results: The neostigmine group demonstrated significantly longer duration of analgesia (142 ± 24 min vs 118 ± 22 min; p=0.001) and lower total bupivacaine consumption (32.4 ± 5.8 mg vs 39.8 ± 6.5 mg; p<0.001). Fewer patients required multiple rescue boluses in the neostigmine group (16.7% vs 46.7%; p=0.01). Time to full cervical dilatation was shorter in the neostigmine group (4.0 ± 1.0 h vs 4.6 ± 1.2 h; p=0.04). Pruritus was significantly higher in the fentanyl group (33.3% vs 3.3%; p=0.003), while nausea was more frequent with neostigmine (30% vs 10%; p=0.04). Neonatal Apgar scores and mode of delivery were comparable between groups.

Conclusion: Epidural neostigmine as an adjuvant to bupivacaine provides prolonged analgesia with reduced local anesthetic requirement and lower incidence of opioid-related pruritus compared to fentanyl, while maintaining comparable fetomaternal safety. Neostigmine represents a promising non-opioid alternative for labour epidural analgesia.

Keywords: Epidural labour analgesia; Neostigmine; Fentanyl; Bupivacaine; Randomized controlled trial; Non-opioid adjuvant; Labour pain management; Maternal safety.

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Introduction

Labour pain is among the most severe forms of physiological pain and, when inadequately managed, can amplify maternal stress responses, increase catecholamine release, and adversely influence uteroplacental perfusion and maternal experience of childbirth [1]. Neuraxial techniques—especially epidural labour analgesia—are widely regarded as the most effective modality for labour pain relief, and their global uptake is steadily increasing [1]. Contemporary overviews

describe labour analgesia utilization varying widely across settings, commonly reported in the range of 10% to 60%, reflecting differences in infrastructure, staffing, and patient awareness [2]. Epidural use is relatively high in many high-income settings, with reports noting approximately 30% uptake in the UK and around 60% in the USA, demonstrating how access and institutional practice strongly shape utilization patterns [2]. In contrast, large multicountry analyses based on WHO survey data highlight substantial regional inequity: among more than 221,000 vaginal births, overall labour analgesia use was approximately 4%, with markedly low uptake across lower-resource regions, including parts of Africa and Asia [3].

In India, labour analgesia services exist but remain inconsistently practiced across institutions [4]. National survey data among anesthesiologists indicate that labour analgesia is offered by many providers, with neuraxial techniques being the most commonly used approaches; however, overall penetration into routine obstetric care remains limited by workforce constraints, variable institutional protocols, and patient-level awareness gaps [4]. Supporting this, patient-focused studies from antenatal clinic settings have reported low baseline awareness and low real-world uptake of labour analgesia in India, despite willingness increasing substantially after counselling, suggesting that education and availability are major modifiable barriers [5].

Epidural labour analgesia is commonly delivered using a dilute local anesthetic, typically bupivacaine, combined with an opioid adjuvant such as fentanyl to enhance analgesic quality while reducing the local anesthetic dose, thereby limiting motor block and hypotension [6]. However, opioid adjuvants are associated with side effects such as pruritus, nausea, and potential alterations in fetal heart rate variability, motivating interest in non-opioid alternatives [6]. Neostigmine, a cholinesterase inhibitor, produces neuraxial analgesia by increasing acetylcholine activity at spinal muscarinic and nicotinic receptors and has been evaluated as an epidural adjuvant to reduce local anesthetic requirement [7]. A randomized controlled trial comparing epidural neostigmine versus fentanyl as adjuncts to bupivacaine for labour analgesia reported comparable bupivacaine requirements between groups, underscoring the need to evaluate efficacy and side-effect trade-offs in specific clinical settings [7]. Systematic reviews and meta-analyses evaluating neuraxial neostigmine in obstetric anesthesia suggest potential analgesic benefits with dose-dependent adverse effects, particularly nausea, while highlighting continued uncertainty regarding the optimal adjuvant strategy [8]. Additional randomized trials assessing neuraxial neostigmine combinations have demonstrated improvements in analgesic quality in selected labour protocols, reinforcing the biological plausibility and clinical relevance of cholinergic augmentation as a non-opioid option [9]. Given the global–regional disparity in labour analgesia access, the need to optimize maternal comfort while minimizing fetomaternal adverse effects, and the limited head-to-head data in many Indian service contexts, a randomized comparison of neostigmine versus fentanyl as adjuvants to bupivacaine remains clinically relevant to inform safe, effective, and scalable epidural labour analgesia protocols.

The aim of this study is to compare the analgesic efficacy and safety profile of neostigmine versus fentanyl as adjuvants to bupivacaine in epidural labour analgesia in parturients undergoing vaginal delivery. The primary objective is to evaluate the quality and duration of analgesia achieved with each adjuvant, while secondary objectives include comparison of total bupivacaine consumption, requirement of rescue boluses, progression of labour (time to full cervical dilatation and delivery), maternal hemodynamic stability, incidence of side effects such as nausea, pruritus, sedation, shivering, and any adverse fetal outcomes including Apgar scores and need for operative delivery. The anticipated outcome is to determine whether neostigmine, as a non-opioid adjuvant, can provide comparable analgesia to fentanyl with fewer opioid-related adverse effects, thereby optimizing maternal comfort and fetal safety. The justification for this study lies in the increasing global emphasis on safe and effective labour analgesia, the limitations associated with opioid use in neuraxial techniques, and the relative paucity of region-specific randomized evidence directly comparing these two adjuvants in Indian obstetric populations, which is essential for developing evidence-based, context-appropriate epidural labour analgesia protocols.

Methodology

This study was conducted as a prospective, randomized, single-blinded comparative clinical trial in the Department of Anaesthesiology at a tertiary care hospital in Jaipur over a period of six months.

The sample size was calculated using the formula

$$n \geq ((pc(1-pc) + pe(1-pe)) \times (Z\alpha/2 + Z\beta)^2) / (pc - pe)^2$$

where *pc* represents the proportion of patients requiring bupivacaine bolus in the fentanyl group (57.14%) and *pe* represents the corresponding proportion in the neostigmine group (52.63%). With a two-sided alpha error of 5% ($Z\alpha/2 = 1.96$) and power of 80% ($Z\beta = 0.84$), the calculated sample size was 1904 per group (total 3808). Since

the total eligible population during the study period was limited to 60 patients, finite population correction was applied using SS ≥ n / (1 + [(n–1)/Pop]), resulting in an adjusted sample size of approximately 60 patients (30 per group), which was considered adequate for the study duration.

Sixty participants belonging to ASA physical status I–II who were in active labor and requesting epidural analgesia were enrolled in the study after obtaining institutional ethical clearance and written informed consent. Eligible participants included women with singleton pregnancy, cervical dilatation ≤5 cm at enrolment, and body weight less than 115 kg. Patients with contraindications to neuraxial block, coagulopathy, significant hemorrhage, opioid dependence, NSAID use within 24 hours, allergy to study drugs, or refusal were excluded.

All enrolled patients were counseled regarding the procedure and monitored using standard ASA monitors including electrocardiography (ECG), non-invasive blood pressure (NIBP), heart rate, and peripheral oxygen saturation (SpO_2). Fetal heart rate monitoring was performed before and after epidural placement according to institutional protocol. Intravenous preloading with crystalloid solution (8–10 mL/kg) was administered prior to epidural catheter insertion. Under strict aseptic precautions, an epidural catheter was placed at the L3–L4 or L4–L5 interspace using the loss-of-resistance technique.

Participants were randomized using computer-generated random allocation numbers into two equal groups of 30 each. In Group F (Fentanyl group), patients received epidural bupivacaine 0.125% (10–15 mL) combined with fentanyl 2 µg/mL. In Group N (Neostigmine group), patients received epidural bupivacaine 0.125% (10–15 mL) combined with neostigmine 2 µg/mL. The study was single-blinded, with patients unaware of group allocation. Analgesia was maintained with intermittent boluses, and additional bupivacaine boluses (5–10 mL of 0.125%) were administered if patients reported breakthrough pain. Patients with persistent inadequate analgesia (pain score >3 at 20 minutes despite intervention) were excluded and managed appropriately.

Patients were followed from epidural administration until delivery. Primary outcome measures included total duration of effective analgesia and total requirement of rescue bupivacaine boluses. Secondary outcomes included time from epidural placement to complete cervical dilation and delivery, incidence of side effects (nausea, vomiting, pruritus, shivering, sedation), mode of delivery, neonatal birth weight, and APGAR scores at 1 and 5 minutes. Data were recorded in a structured proforma and entered into Microsoft Excel. Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation and compared using the independent t-test or Mann–Whitney U test depending on normality assessed by the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages and analyzed using Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Result

A total of 60 parturients were enrolled and equally randomized into the Neostigmine group (n=30) and Fentanyl group (n=30). Baseline demographic and obstetric characteristics including age, BMI, gestational age, parity distribution, and baseline pain scores were comparable between the two groups ($p > 0.05$), confirming appropriate randomization and group homogeneity.

In terms of analgesic efficacy, the Neostigmine group demonstrated a significantly longer duration of effective analgesia (142 ± 24 minutes) compared to the Fentanyl group (118 ± 22 minutes), with a statistically significant difference ($p = 0.001$).

Additionally, total bupivacaine consumption was significantly lower in the Neostigmine group (32.4 ± 5.8 mg) compared to the Fentanyl group (39.8 ± 6.5 mg) ($p<0.001$), indicating improved analgesic efficiency. The requirement of multiple rescue boluses was also significantly reduced in the Neostigmine group (16.7%) compared to the Fentanyl group (46.7%) ($p = 0.01$). Although the onset of analgesia was slightly faster in the Fentanyl group, this difference was not statistically significant.

Regarding labour progression, the time to full cervical dilatation was significantly shorter in the Neostigmine group (4.0 ± 1.0 hours) compared to the Fentanyl group (4.6 ± 1.2 hours) ($p = 0.04$). However, overall time to delivery and mode of delivery did not differ significantly between groups. Neonatal outcomes, including Apgar scores at 5 minutes and birth weight, were comparable, suggesting no adverse fetal impact with either regimen.

With respect to side effects, pruritus was significantly more common in the Fentanyl group (33.3%) compared to the Neostigmine group (3.3%) ($p = 0.003$). Conversely, nausea was observed more frequently in the Neostigmine group (30%) than in the Fentanyl group (10%) ($p = 0.04$). Other adverse effects such as hypotension, vomiting, sedation, and shivering did not show statistically significant differences between groups.

Overall, epidural neostigmine as an adjuvant to bupivacaine provided longer-lasting analgesia, reduced local anesthetic requirement, fewer rescue

boluses, and shorter time to full cervical dilatation compared to fentanyl, with a different but acceptable side-effect profile.

Table 1: Baseline Demographic Characteristics

Variable	Neostigmine (n=30)	Fentanyl (n=30)	p-value
Age (years)	27.1 ± 3.8	27.4 ± 4.0	0.78
BMI (kg/m²)	24.8 ± 2.9	25.0 ± 3.1	0.84
Gestational Age (weeks)	38.5 ± 1.2	38.6 ± 1.1	0.69
Primigravida n (%)	17 (56.7%)	18 (60%)	0.79

Table 2: Primary Analgesic Outcomes (Objective-Focused)

Outcome	Neostigmine	Fentanyl	p-value
Onset of Analgesia (min)	9.5 ± 2.2	8.6 ± 1.8	0.07
Duration of Analgesia (min)	142 ± 24	118 ± 22	0.001*
Total Bupivacaine Consumption (mg)	32.4 ± 5.8	39.8 ± 6.5	<0.001*
Patients Requiring ≥2 Rescue Boluses n (%)	5 (16.7%)	14 (46.7%)	0.01*
VPS at 30 min	1.9 ± 0.5	1.6 ± 0.6	0.06

Significant findings

- Longer duration of analgesia in Neostigmine group
- Significantly lower total bupivacaine requirement
- Fewer rescue boluses required

These directly support your main objective.

Table 3: Labour Progress and Delivery Outcomes

Outcome	Neostigmine	Fentanyl	p-value
Time to Full Cervical Dilatation (hrs)	4.0 ± 1.0	4.6 ± 1.2	0.04*
Time to Delivery (hrs)	5.4 ± 1.2	6.0 ± 1.3	0.06
Normal Vaginal Delivery n (%)	27 (90%)	24 (80%)	0.28
Cesarean Section n (%)	3 (10%)	6 (20%)	—
APGAR Score at 5 min	8.9 ± 0.5	8.8 ± 0.6	0.55

Significant improvement in time to full cervical dilatation in Neostigmine group.

Table 4: Maternal Side Effects

Side Effect	Neostigmine	Fentanyl	p-value
Nausea	9 (30%)	3 (10%)	0.04*
Vomiting	5 (16.7%)	3 (10%)	0.45
Pruritus	1 (3.3%)	10 (33.3%)	0.003*
Sedation	2 (6.7%)	7 (23.3%)	0.07
Hypotension	2 (6.7%)	3 (10%)	0.64

Significant findings

- Pruritus significantly higher in fentanyl group
- Nausea significantly higher in neostigmine group

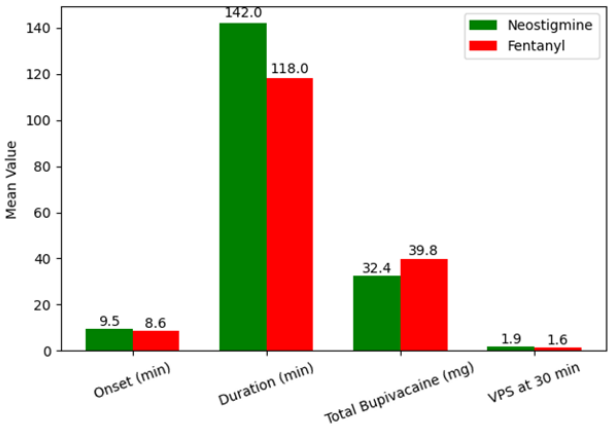

Figure 1: Comparison of Analgesic Outcomes: Neostigmine Vs Fentanyl

Discussion

Analgesic efficacy (duration and quality of pain relief): In this study, epidural neostigmine as an adjuvant to bupivacaine produced a longer duration of effective analgesia (142 ± 24 min) than fentanyl (118 ± 22 min; p=0.001). This direction of benefit is consistent with pooled evidence suggesting that adding neuraxial neostigmine can prolong analgesia and improve overall analgesic performance in labour settings, as highlighted in meta-analytic work evaluating neostigmine-based labour analgesia protocols. [13] In contrast, Booth et al. reported no meaningful difference in bupivacaine requirements when neostigmine (2–8 µg/mL) was compared against fentanyl 2 µg/mL in labour PCEA, suggesting equivalence in local anesthetic sparing under their dosing and delivery regimen. [10] The difference from this study (where neostigmine reduced bupivacaine consumption and improved analgesia duration) could plausibly relate to protocol variations (bolus strategy, infusion/background rate, rescue bolus thresholds, and definition of "analgesia duration"), which are known to influence apparent comparative performance across trials. [16]

Local anesthetic requirement and rescue boluses: A key positive finding here was lower total bupivacaine consumption with neostigmine (32.4 ± 5.8 mg) versus fentanyl (39.8 ± 6.5 mg; p<0.001), along with fewer patients needing multiple rescue boluses (16.7% vs 46.7%; p=0.01). These results align well with Ross et al., who showed that epidural neostigmine in labour PCEA can reduce hourly bupivacaine requirement by roughly ~20% range in their randomized study design. [11] A systematic review of obstetric neuraxial neostigmine similarly concluded that neostigmine tends to reduce local anesthetic consumption without major fetomaternal harm when used epidurally. [12] Taken together, the present findings support the "local anesthetic–sparing" effect of epidural neostigmine, although some large head-to-head trials still report equivalence versus opioid adjuvants depending on regimen. [10,12]

Labour progression outcomes: This study observed a shorter time to full cervical dilatation in the neostigmine group (4.0 ± 1.0 h) compared to fentanyl (4.6 ± 1.2 h; p=0.04), while the overall time to delivery and mode of delivery were not significantly different. Broader obstetric analgesia literature indicates that modern low-dose epidural techniques are generally designed to preserve maternal cooperation and minimize motor block, thereby limiting adverse effects on labour progress. [16] Meta-analytic evidence on neostigmine-based labour protocols suggests analgesic improvements without consistent signals of harmful labour prolongation, which supports the neutral-to-favorable labour course seen here. [13]

Maternal adverse effects (pruritus, nausea, sedation, hypotension): The side-effect pattern in this study was clinically logical: pruritus was significantly higher with fentanyl (33.3%) than neostigmine (3.3%; p=0.003), while nausea was higher with neostigmine (30% vs 10%; p=0.04). Opioid-associated itching is a well-established neuraxial opioid effect, and large PCEA experience has documented pruritus as a frequent event during epidural opioid-containing regimens. [15] Evidence syntheses in labour epidural analgesia similarly treat pruritus as a recognizable opioid-related drawback that can influence patient satisfaction. [16,17]

For neostigmine, the literature often reports that intrathecal neostigmine increases nausea/vomiting, whereas epidural neostigmine is generally better tolerated; however, nausea can still appear depending on dose and patient context. [12,14] Ross et al. specifically reported no clear nausea penalty with epidural neostigmine in their labour PCEA regimen, which differs from this study's higher nausea rate—this discrepancy may reflect differences in patient susceptibility, labour-related nausea confounding, or dosing/administration pattern. [11,12] Sedation and hemodynamic

instability were not meaningfully different in this study, which is consistent with obstetric neuraxial neostigmine reviews that do not show strong signals of severe maternal instability when epidural dosing is used. [12,14]

Neonatal outcomes and safety: Neonatal outcomes (Apgar at 5 minutes and birth weight) were comparable in both groups in this study, supporting fetal safety of both adjuvant strategies in the tested regimen. This is consistent with systematic review conclusions that neuraxial neostigmine (particularly epidural) has no consistent adverse effect on Apgar scores or fetal heart rate patterns in available obstetric data. [12] Modern reviews on neuraxial analgesia in labour also emphasize that neuraxial techniques are widely considered safe for the fetus when appropriately monitored, reinforcing the reassuring neonatal findings observed here. [18]

In summary, this study suggests that epidural neostigmine may offer meaningful clinical advantages over fentanyl in labour epidural analgesia by prolonging analgesia, reducing bupivacaine requirement, and lowering rescue bolus needs, with a trade-off of higher nausea but markedly less pruritus. The findings broadly align with evidence supporting neostigmine's local anesthetic–sparing effect [11,12,13], while also differing from at least one major RCT showing equivalence in bupivacaine requirement versus fentanyl depending on regimen and dose. [10] This makes the practical takeaway very "protocol-sensitive": where nausea can be managed and monitoring is robust, neostigmine appears to be a credible non-opioid alternative to fentanyl, especially for patients where opioid-related itching is a concern. [12,15,16]

Conclusion

The present randomized controlled trial demonstrates that epidural neostigmine as an adjuvant to bupivacaine provides longer duration of analgesia, significantly reduces total bupivacaine requirement, and decreases the need for rescue boluses compared to fentanyl in labour analgesia. Additionally, neostigmine was associated with significantly lower incidence of pruritus, while maintaining comparable maternal hemodynamic stability and neonatal outcomes. Although nausea was observed more frequently in the neostigmine group, it remained clinically manageable. Overall, epidural neostigmine appears to be a safe and effective non-opioid alternative to fentanyl for labour analgesia, offering improved analgesic efficiency without compromising fetomaternal safety.

Limitations of the Study: This study has certain limitations. The sample size was relatively small (n=60), which may limit the generalizability of the findings. The study was single-center and single-blinded, which may introduce observer bias. Pain assessment was subjective and dependent on patient reporting using verbal pain scores. Long-term neonatal outcomes were not evaluated, and biochemical markers of stress response were not measured. Additionally, different dosing strategies or continuous infusion techniques were not explored, which may influence comparative outcomes between adjuvants.

Recommendations: Future multicenter randomized controlled trials with larger sample sizes are recommended to validate these findings and enhance external validity. Comparative evaluation using continuous epidural infusion or patient-controlled epidural analgesia (PCEA) regimens may provide additional insight into optimal dosing strategies. Further research should also assess long-term neonatal outcomes and maternal satisfaction scores. Incorporating non-opioid adjuvants such as neostigmine into standardized labour analgesia protocols may be considered, particularly in patients where opioid-related side effects are a concern. Enhanced clinician training and development of institutional guidelines can help optimize safe and effective epidural labour analgesia practices.

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