Section: Anaesthesiology

Original Research Article

EFFECT OF ADDING TWO DIFFERENT DOSES OF NALBUPHINE TO LEVOBUPIVACAINE IN PATIENTS UNDERGOING LOWER LIMB ORTHOPAEDIC SURGERY UNDER SUBARACHNOID BLOCK: A PROSPECTIVE RANDOMIZED STUDY

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ABSTRACT

Background: Levobupivacaine is a safer alternative to bupivacaine for spinal anaesthesia due to its reduced cardiotoxicity. Nalbuphine, a κ-agonist and μ-antagonist opioid, is increasingly used as an intrathecal adjuvant to enhance analgesia while minimizing μ-opioid-related side effects. However, limited data exist comparing different doses of intrathecal nalbuphine when combined with levobupivacaine for orthopaedic surgeries. The objective is to compare the effects of two different doses of nalbuphine (0.4 mg and 0.6 mg) added to 15 mg of 0.5% isobaric levobupivacaine on sensory and motor block characteristics, analgesic efficacy, and side-effect profile in patients undergoing lower limb orthopaedic surgery under subarachnoid block. **Materials and Methods:** This prospective, randomized, double-blind study included 39 ASA I/II patients undergoing lower limb orthopaedic surgery. Patients were assigned to receive either 0.4 mg (Group A) or 0.6 mg (Group B) of nalbuphine with 15 mg of isobaric levobupivacaine. The primary outcome was the duration of adequate analgesia (time to VAS ≥3). Secondary outcomes included the onset and duration of sensory and motor block, hemodynamic changes, sedation, and side effects. Statistical analysis was performed using SPSS v20.0, with $p<0.05$ considered significant. **Result:** Demographic and surgical variables were comparable between groups. There was no statistically significant difference in sensory or motor block onset, block height, two-segment regression time, or duration of adequate analgesia between groups. Both groups showed stable intraoperative and postoperative hemodynamic profiles. No respiratory depression or serious adverse effects were reported. Mild sedation (score ≤2) was observed in all patients. **Conclusion:** When added to levobupivacaine, both 0.4 mg and 0.6 mg intrathecal nalbuphine provided effective anaesthesia and prolonged postoperative analgesia without significant differences in efficacy or adverse effects. The 0.4 mg dose may be preferable due to its similar effectiveness and lower potential for dose-related side effects.

INTRODUCTION

Spinal anaesthesia (SA) has evolved significantly since Karl August Bier first administered it to a human subject in 1898 at the Royal Surgical Hospital, University of Kiel, Germany. Due to its simplicity, safety, and efficacy, it is now a widely accepted and routinely employed technique for lower limb and infra-umbilical surgeries.[1] SA offers rapid onset, reliable sensory and motor blockade, excellent intraoperative muscle relaxation, and prolonged postoperative analgesia without inducing loss of consciousness. Its advantages over general anaesthesia include shorter hospital stays, early ambulation, reduced postoperative complications, and fewer systemic side effects.[2] Among various local anaesthetic (LA) agents used for subarachnoid block (SAB), levobupivacaine—a pure S(-) enantiomer of bupivacaine—has gained prominence due to its favourable safety profile. While racemic bupivacaine is effective, it carries a higher risk of cardiac toxicity, such as hypotension, arrhythmias, and even life-threatening events. With its high protein-binding affinity, Levobupivacaine produces selective sensory blockade with fewer

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cardiovascular and central nervous system side effects, making it a preferred choice in ambulatory and regional anaesthesiapractices.[3]

To enhance the quality and duration of SAB, adjuvants like opioids and non-opioid agents are frequently combined with LAs. Among these, nalbuphine—a semisynthetic opioid with mixed μ-antagonist and κ-agonist activity—has shown promise in enhancing analgesic efficacy without the adverse effects typically associated with μ-opioid agonists such as morphine or fentanyl, which include respiratory depression, pruritus, nausea, and vomiting. Nalbuphine's unique receptor profile allows it to prolong sensory analgesia without significantly affecting motor block or sympathetic function.[4] Moreover, its lack of addictive potential and limited side-effect profile make it a valuable adjuvant, particularly in the context of spinal anaesthesia. Although nalbuphine has been investigated in varying doses (0.2–2.4 mg) as an intrathecal adjuvant with different LAs, there remains a paucity of data comparing different doses of nalbuphine when added to levobupivacaine for orthopaedic procedures.[4-6] The current study was therefore designed to compare the effect of two different doses of intrathecal nalbuphine (0.4 mg and 0.6 mg) as adjuvants to 15 mg of 0.5% levobupivacaine in patients undergoing lower limb orthopaedic surgeries under subarachnoid block.

MATERIALS AND METHODS

This prospective, randomized, double-blind, controlled study was conducted in the Department of Anaesthesiology, Critical Care and Pain Medicine at the University College of Medical Sciences and GTB Hospital, Delhi, after obtaining approval from the Institutional Ethical Committee (Human Research). The trial was registered prospectively with the Clinical Trials Registry of India (CTRI). The study spanned from November 2018 to April 2020. Patients aged 18 to 65 years of the American Society of Anesthesiologists (ASA) physical status I and II undergoing elective lower limb orthopaedic surgeries under spinal anaesthesia were enrolled. Inclusion criteria required patients to be within a height range of 150–180 cm, while patients with contraindications to subarachnoid block, hypersensitivity to study drugs, or a BMI >30 kg/m² were excluded. A minimum of 20 patients were allocated to each group, based on sample size calculation using prior study data, assuming a standard deviation of 16.2 minutes in duration of analgesia and a detectable mean difference of 20–30 minutes at 90% power and 5% significance.

All patients underwent pre-anaesthetic assessment a day prior to surgery. Written informed consent was obtained, and they were familiarized with the Visual Analogue Scale (VAS) for pain assessment. Standard fasting protocols and premedication with alprazolam 0.25 mg were followed. Standard monitoring (ECG, SpO_2, NIBP) was applied in the operating theatre, and intravenous access was secured. Patients were preloaded with Ringer's lactate (10 ml/kg). Using a computer-generated randomization table, patients were assigned to one of two groups: Group A received 15 mg of 0.5% levobupivacaine with 0.4 mg nalbuphine hydrochloride (total volume 3.3 ml); Group B received 15 mg of 0.5% levobupivacaine with 0.6 mg nalbuphine (3.3 ml total). The drug was prepared by an independent anesthesiologist not involved in patient care or data collection, ensuring double-blinding.

Spinal anaesthesia was performed in a sitting position under aseptic precautions at the L2–L3 or L3–L4 interspace using a 25G Quincke's spinal needle. After confirming free CSF flow, 3.3 ml of the study drug was injected intrathecally over 15 seconds. Patients were then positioned supine and administered oxygen via facemask. Sensory block height was assessed using a pin-prick method, and motor block using the Modified Bromage Scale. Parameters recorded included onset time of sensory and motor blocks, highest sensory level achieved, time for two-segment regression, and duration of effective analgesia (defined as time from spinal injection to VAS ≥3). Sedation was assessed using the University of Michigan Sedation Scale. Hemodynamic variables, side effects (e.g., hypotension, bradycardia, nausea), and need for rescue analgesia (IV paracetamol 1 g) were recorded at specified intervals intraoperatively and postoperatively. Statistical analysis was performed using SPSS v20. Continuous variables were analyzed using Student's t-test or Mann-Whitney U test, categorical variables using Chi-square/Fisher's exact test, and repeated measures using ANOVA. A p-value <0.05 was considered statistically significant.

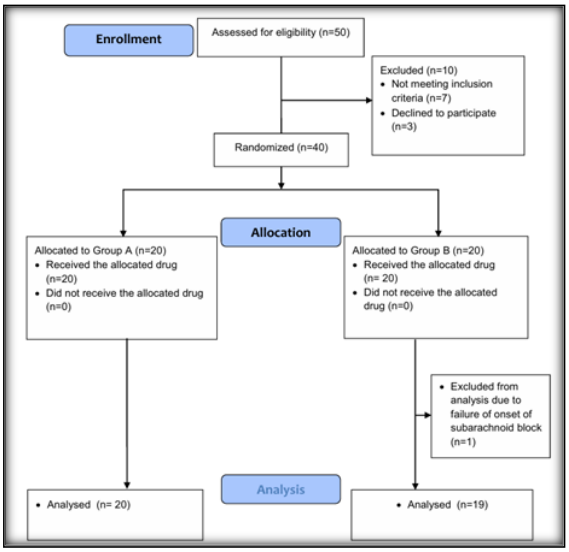

Figure 1: Consort flow diagram

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RESULTS

A total of 50 patients were assessed for eligibility. Seven patients did not meet the inclusion criteria, and three declined to participate. The remaining 40 patients were randomized into two equal groups (n=20). One patient in Group B experienced a failed subarachnoid block and was excluded from the final analysis. Thus, data from 39 patients (Group A: n=20, Group B: n=19) were included, as outlined in the CONSORT flow diagram.

The demographic variables, including age, weight, and height, were comparable between the two groups. Of the 39 patients, 33 were male, and six were female, with a similar gender distribution across both groups. The American Society of Anesthesiologists (ASA) physical status classification (I/II) and duration of surgery were also comparable between the groups [Table 1].

The onset time of sensory block, maximum sensory block height achieved, and time to two-segment regression were not significantly different between the two groups. The duration of adequate analgesia was comparable across groups. Similarly, the mean onset time and duration of motor blockade showed no statistically significant difference. The Modified Bromage Scale (MBS) scores were similar throughout the intraoperative and postoperative periods.

The mean heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were comparable between Group A and Group B at all recorded intraoperative time points. Within-group analysis revealed a significant decrease in heart rate from 15 minutes to 90 minutes in Group A, while in Group B, the reduction in heart rate was significant at 45, 60, 75, and 90 minutes compared to baseline. SBP showed a statistically significant decline from 5 to 90 minutes post-block in both groups relative to their respective baseline values, although no significant inter-group differences were observed. A significant reduction in DBP was also noted within both groups—beginning at 10 minutes in Group A and 5 minutes in Group B—persisting until 90 minutes post-block. Additionally, a statistically significant difference in mean DBP was observed between the two groups. Mean arterial pressure decreased significantly from 5 to 90 minutes in both groups compared to baseline, but the difference between groups remained non-significant. Respiratory rates were similar across the two groups throughout the study; however, Group A significantly decreased at 75 and 90 minutes, whereas Group B showed reductions at 30, 45, 75, and 90 minutes compared to their respective baselines.

Intraoperative sedation scores assessed using the University of Michigan Sedation Scale remained ≤2 in all patients, with no significant difference between groups. Postoperatively, sedation scores remained within the same range and were comparable between groups.

Postoperative pain was evaluated using the Visual Analogue Scale (VAS). Both groups had comparable VAS scores overall. Notably, at 15 and 30 minutes postoperatively, Group B recorded mean VAS scores of 0, while Group A had 0.20 ± 0.70 and 0.25 ± 0.72, respectively, though these differences were not statistically significant. The MBS scores in the postoperative period were also similar between groups.

Hypotension was observed in 5 patients from each group (Group A: 25%; Group B: 26.3%) and was effectively managed with intravenous fluids and mephentermine 6 mg IV. One patient in Group A experienced nausea, which was treated with intravenous ondansetron 4 mg. No other significant adverse effects were reported during the intraoperative or postoperative periods.

Table 1: Demographic profile of study population

Parameter	Group A (n=20)	Group B (n=19)	p-value
Age (Yr)	37.70±11.45	36.47±14.34	0.769
Weight (kg)	64.20±10.20	63.26±11.83	0.792
Height (cm)	167.05±5.62	166.68±6.42	0.851
ASA N (%)			0.648
I	13	11	
II	7	8	
Gender			0.946
Male	17	16	
Female	3	3	
Gender (M:F)		16:03	
Duration of surgery (min)	116.75±20.85	119.21±16.77	0.688
Characteristics of Sensory Block			
Maximum Block height	T7 [T6-T9]	T7 [T5-T8]	0.931
Time of onset of block (min)	10.10±4.58	10.89±4.58	0.591
Time of two segment regression (min)	104.15±18.20	109.74±18.52	0.348
Duration of effective analgesia (min)	215.35±47.08	217.37±42.80	0.89
Motor block			
Onset of motor blockade (min)	4.05±1.76	4.68±2.19	0.324
Duration of motor blockade (min)	252.75±46.30	244.21±33.64	0.516

Table 2: Comparison of Intra operative Parameters Between Group A and Group B.

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Parameter	Baseline	5	10	15	20	25	30	45	60	75	90	
HR												0.936
Group A (n=20)	96.90 ±12.77	94.35± 14.74	94.0±15.94	91.20± 14.76	88.40± 14.97	87.55± 15.84	87.65± 15.53	83.65± 16.70	80.90± 16.42	82.60± 15.09	84.20± 15.39	
Group B (n=19)	92.89 ±17.98	92.63± 17.23	92.32± 17.91	90.53± 19.52	90.68± 20.24	89.68± 19.72	87.74± 18.39	85.42± 15.06	84.21± 15.52	85.53± 15.03	84.16± 13.75	
SBP												0.384
Group A (n=20)	132.70±12.30	126.00 ±12.18	121.95 ±12.62	118.50 ±13.82	118.80 ±12.88	117.55 ±11.65	118.55 ±13.65	114.60 ±10.83	112.15 ±8.88	111.80 ±9.23	111.85 ±11.42	
Group B (n=19)	130.89±11.01	123.16 ±11.32	118.84 ±11.81	114.32 ±16.31	112.89 ±10.41	116.84 ±9.38	114.68 ±9.75	109.63 ±15.40	113.05 ±11.97	111.79 ±11.73	110.16 ±9.69	
DBP												0.023
Group A (n=20)	77.80 ±7.61	75.55± 8.26	72.25± 8.80	70.70± 9.17	71.55± 8.99	70.60± 6.30	72.30± 7.55	69.85± 7.25	68.25± 6.42	68.55± 7.56	70.05± 9.93	
Group B (n=19)	77.11 ±7.75	71.53± 7.46	68.95± 9.50	65.68± 11.80	64.00± 10.41	64.74± 7.20	66.63± 9.32	61.37± 13.04	62.58± 10.56	64.68± 8.56	63.58± 8.68	
MAP												
Group A (n=20)	96.75 ±9.24	91.75± 8.44	88.85± 9.86	87.40± 10.32	88.55± 9.75	86.95± 8.23	88.05± 8.71	85.55± 7.84	83.40± 6.63	82.80± 7.38	84.55± 10.26	0.142
Group B (n=19)	96.26 ±7.62	90.79± 9.36	86.79± 10.80	83.47± 13.73	81.00± 11.36	83.26± 7.49	84.95± 8.95	78.16± 13.99	79.68± 11.33	81.21± 9.73	80.00± 8.41	
Respiratory rate												0.345
Group A (n=20)	17.05 ±2.50	16.95± 2.52	16.80± 3.40	16.85± 2.89	16.80± 2.24	16.55± 2.11	16.15± 2.01	16.30± 2.34	16.20± 2.44	16.00± 2.00	15.75± 2.47	
Group B (n=19)	17.74 ±2.94	17.89± 2.60	17.89± 2.42	17.74± 2.62	17.42± 2.74	17.21± 2.62	16.53± 2.37	16.68± 2.61	16.89± 2.16	16.26± 2.56	16.53± 2.80	
Motor Block [Modified Bromage Scale];Median [Inter-quartile range]												0.158
Group A (n=20)		1.00 [1.00-2.00]	2.00 [2.00-2.00]	2.00 [2.00-3.00]	3.00 [2.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	
Group B (n=19)		1.00 [1.00-1.00]	2.00 [2.00-2.00]	2.00 [2.00-2.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [3.00-3.00]	
Sedation Score												
Mild sedation (score 1)												
Group A (n=20)		0	0	1	6	9	14	13	9	10	9	
Group B (n=19)		0	0	2	4	8	10	8	7	6	6	
Moderate sedation (score 2)												
Group A (n=20)		0	0	0	0	0	0	3	8	6	1	
Group B (n=19)		0	0	0	0	0	1	4	6	6	3	
Deep sedation (score 3/4)												
Group A (n=20)		0	0	0	0	0	0	0	0	0	0	
Group B (n=19)		0	0	0	0	0	0	0	0	0	0	

Table 3: Comparison of Postoperative Parameters Between Group A and Group B

Parameter	15	30	45	60	75	90	
SBP							
Group A (n=20)	117.00±10.69	114.60±12.16	117.90±10.21	114.55±9.99	116.05±11.72	118.90±13.91	0.368
Group B (n=19)	117.39±7.78	117.00±9.73	117.94±9.12	120.94±7.63	119.56±8.86	120.72±8.72	
DBP							0.649
Group A (n=20)	70.85±9.35	69.95±10.20	71.85±6.39	69.15±7.04	70.75±7.97	72.15±9.37	
Group B (n=19)	65.28±6.99	66.72±8.42	68.56±7.69	72.72±8.96	72.61±8.89	73.00±9.17	
MAP							0.90

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Group A (n=20)	86.60±9.03	85.15±9.76	88.30±6.81	85.50±6.74	87.25±7.69	88.05±9.98	4
Group B (n=19)	83.17±5.97	84.06±7.26	84.89±7.43	90.00±6.15	88.72±7.51	88.67±8.83	
RR							0.757
Group A (n=20)	16.05±2.56	16.35±3.18	16.35±2.85	16.20±2.48	16.40±1.98	16.00±2.13	
Group B (n=19)	16.17±2.36	15.61±2.59	15.83±2.55	16.17±2.60	16.00±2.50	16.17±2.55	
SEDATION SCORE							
Mild Sedation							
Group A (n=20)	1	1	4	2	4	2	
Group B (n=19)	0	0	6	2	2	1	
Moderate Sedation							
Group A (n=20)	0	0	1	5	1	1	
Group B (n=19)	0	0	0	2	1	0	
Deep Sedation							
Group A (n=20)	0	0	0	0	0	0	
Group B (n=19)	0	0	0	0	0	0	
VAS							0.754
Group A (n=20)	0.20±0.70	0.25±0.72	0.60±1.05	0.50±0.83	0.50±0.76	0.85±1.09	
Group B (n=19)	0	0	0.37±0.76	1.05±1.43	0.94±1.21	1.00±0.97	
Modified Bromage Scale (MBS)							0.729
Group A (n=20)	3.00 [3.00-3.00]	3.00 [2.00-3.00]	3.00 [2.00-3.00]	2.00 [2.00-3.00]	2.00 [2.00-3.00]	2.00 [1.00-3.00]	
Group B (n=19)	3.00 [3.00-3.00]	3.00 [3.00-3.00]	3.00 [2.00-3.00]	2.00 [2.00-3.00]	2.00 [2.00-2.00]	2.00 [1.00-2.00]	

DISCUSSION

Lower limb fractures constitute a significant proportion of orthopaedic surgical cases, and subarachnoid block (SAB) remains a preferred anaesthetic technique due to its safety, efficacy, and ability to provide rapid onset of anaesthesia with excellent intraoperative and postoperative analgesia. Compared to general anaesthesia, SAB offers advantages such as early mobilization, reduced hospital stay, and fewer systemic side effects. Levobupivacaine, a pure S(-) enantiomer of bupivacaine, is increasingly favoured due to its reduced cardiotoxic and neurotoxic potential. Nalbuphine, a semisynthetic opioid with κ-agonist and μ-antagonist activity, provides adequate analgesia with a lower risk of common μ-opioid-related side effects such as pruritus and respiratory depression. In this prospective, randomized, double-blind study, we compared the effect of two doses of intrathecal nalbuphine (0.4 mg and 0.6 mg) when added to isobaric levobupivacaine in ASA I/II patients undergoing lower limb orthopaedic surgery. Demographic and surgical variables were comparable between the two groups, and both regimens provided adequate anaesthesia for the planned procedures.

The onset of sensory block to the T10 level was comparable between groups and consistent with previous findings by Vanna et al. and Naithani et al., while Mehta et al. and Jindal et al. reported earlier and delayed onsets, respectively.[7-10] This variability may be explained by the density and dose of the local anaesthetic and patient positioning, as isobaric solutions have a less predictable spread than hyperbaric agents.[11] In our study, the median maximum block height was T7 in both groups, which aligns with the findings of Lee et al., Jindal et al., and Vellosillo et al., although Vanna et al. reported a lower T9 level.[7,10,12,13] Our results also showed that adding nalbuphine did not significantly alter block height, which agrees with Mukherjee et al.[14] The time to two-segment regression was significantly prolonged in both groups when compared to studies using levobupivacaine alone, suggesting that nalbuphine effectively extends sensory block duration.[10,15] Although our results differed from some studies using bupivacaine or higher nalbuphine doses, they remain consistent with findings by Gupta et al. using a nalbuphine-LA combination.[14,16-18]The duration of adequate analgesia was similar in both groups and aligns with observations by Attri et al. and Culebras et al.[19,20] Longer durations reported by Bindra et al. and Jyothi et al. may be attributed to differences in nalbuphine dose and the local anaesthetic used.[21,22] Motor block characteristics were also comparable, with no significant difference in onset or duration between the groups. Our findings are consistent with earlier studies, indicating that low-dose nalbuphine does not delay motor onset.[7,14,16,23] The duration of the motor block was similar to previous reports, though Jindal et al. observed a longer duration.[10,24] Complete motor block was achieved in all patients within 20 minutes, and surgeons reported satisfactory muscle relaxation. Importantly, no patient experienced respiratory depression, consistent with the known ceiling effect of nalbuphine on respiratory depression due to its μ-antagonist action, similar to findings by Ahluwalia et al., Culebras et al., and others.[16,20,24-26] Sedation remained within acceptable limits and did not exceed a score of 2, supporting findings by Shakooh et al. and Jyothi et al., who also reported mild, desirable sedation with intrathecal nalbuphine.[22,27]Hemodynamically, both groups remained stable throughout, with only minor reductions in DBP in group B that required no intervention—similar to the trends reported by Culebras et al. and Hoda et al.[20,23] Postoperative

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pain scores and vital parameters were comparable, with no serious adverse effects observed.

CONCLUSION

The addition of nalbuphine as an intrathecal adjuvant to 0.5% isobaric levobupivacaine in patients undergoing lower limb orthopaedic surgeries under subarachnoid block resulted in adequate anaesthesia, satisfactory sensory and motor block characteristics, and prolonged postoperative analgesia without significant adverse effects. Both doses of nalbuphine (0.4 mg and 0.6 mg) were equally effective regarding block onset, block height, duration of analgesia, and hemodynamic stability. No significant advantage was observed with the higher dose of 0.6 mg, suggesting that 0.4 mg may be preferable due to its similar efficacy and potentially lower risk of dose-related side effects. Thus, nalbuphine at a dose of 0.4 mg appears to be a safe and effective adjuvant to levobupivacaine for spinal anaesthesia in lower limb orthopaedic procedures.

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