

A randomized comparative study of epidural ropivacaine 0.2% with adjuvant fentanyl or nalbuphine for post-operative analgesia in lower limb surgeries



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ABSTRACT

Background: Opioid analgesics with local anesthetics in an epidural route are extremely safe, effective, and reliable methods of post-operative pain relief. **Aims and Objectives:** The primary objective is to compare the duration of analgesia and pain scoring by visual analog scale. The secondary objective is to monitor sedation, hemodynamic changes, and side effects such as nausea, vomiting, shivering, and pruritus. **Materials and Methods:** A prospective randomized comparative study of 0.2% ropivacaine with nalbuphine and 0.2% ropivacaine with fentanyl in epidural route for post-operative analgesia in elective lower limb surgeries under spinal anesthesia was carried out in a population of 80 patients. After 1 ½ h of surgery under spinal anesthesia, patients in group RF received 10 mL of 0.2% ropivacaine with 25 mcg of fentanyl and those in group RN received 10 mL of 0.2% ropivacaine with 2.5 mg of nalbuphine and were observed for the study parameters over time. **Results:** The mean duration of analgesia was longer in group RN than in group RF (398.45 vs. 222.88 min). The hemodynamic parameters such as heart rate, mean arterial pressure, and respiratory rate were statistically significant from 240 to 480 min which is 4–6 h in group RF and 6–8 h in group RN. 27.5% of patients in group RN attained sedation whereas 7.5% of subjects in group RF had a sedation score of 2 and above at 30 min. The subjects in group RN had a lower visual analog score than group RF. 12% and 4% of patients had vomiting in group RN and group RF, respectively. **Conclusion:** Epidural nalbuphine in a dose of 2.5 mg with 0.2% ropivacaine provided a longer duration of analgesia with better pain score and more sedation which was advantageous for post-operative patient compliance and satisfaction as compared to 25 mcg of fentanyl with 0.2% ropivacaine.

Key words: Epidural analgesia; Ropivacaine; Nalbuphine; Fentanyl

INTRODUCTION

Epidural anesthesia for lower limb orthopedic surgeries provides not only perioperative surgical anesthesia but also post-operative analgesia.^{1,2} Epidural anesthesia reduces stress related to surgery, improves surgical outcome, provides adequate post-operative pain relief,

and is helpful in early ambulation of the patient as well as hospital discharge. Inadequate post-operative pain relief can increase the patient's stress, morbidity, and mortality.

Ropivacaine, a newer amide local anesthetic widely used during epidural analgesia, has minimal cardiovascular and central nervous system toxicity as well as a lesser propensity

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for motor block.^{3,4} Adjuvants added to local anesthetics for post-operative analgesia prolong the duration of action, produce the early onset of action, better sedation, and maintain stable hemodynamics. Fentanyl a synthetic opioid used as an adjunct to local anesthetics for epidural analgesia provides a dose-sparing effect of local anesthetics and superior analgesia.^{5,6} There is an increased chance of side effects such as nausea, vomiting, pruritus, urinary retention, and respiratory depression.^{7,8} Nalbuphine an agonist-antagonist opioid acts as an antagonist at the μ -receptor and an agonist at the κ -receptor. Activation of supraspinal and spinal κ -receptors results in limited analgesia, respiratory depression, and sedation. Nalbuphine is administered as an analgesic supplement for conscious sedation or balanced anesthesia and post-operative and chronic pain relief. For post-operative epidural analgesia, nalbuphine resulted in a lower incidence of nausea and decreased need for bladder catheterization.⁹

Manoj Prabhakar *et al.*,¹⁰ in a randomized double-blind study compared the post-operative analgesia, hemodynamic variations, and side effects of epidural administration of nalbuphine versus fentanyl as an adjuvant to bupivacaine in elective lower limb surgeries and found that the mean duration of analgesia was longer in nalbuphine group (387.83 ± 38.32 min) compared to fentanyl group (343.60 ± 25.64 min). Kumar *et al.*,¹¹ compared epidural butorphanol versus nalbuphine as an adjuvant to ropivacaine in 60 adult patients in lower limb orthopedic surgeries under combined spinal epidural anesthesia and found that the onset of analgesia was earlier in nalbuphine group (1.45 ± 0.51 min) followed by butorphanol group (4.45 ± 0.61 min) and the duration of analgesia was significantly prolonged in nalbuphine group (6.40 ± 0.821 h) than butorphanol group (4.45 ± 0.605 h). Shelke *et al.*,¹² in a randomized prospective double-blind study involving 40 patients compared epidural nalbuphine or fentanyl to 2% ropivacaine and found that the pain score was comparable in both the groups, but the number of rescue analgesics requirement was higher in nalbuphine group than fentanyl group. Hence this study was conducted to compare the post-operative analgesic effect of nalbuphine and fentanyl as an adjuvant to epidural ropivacaine 0.2% in adult patients undergoing lower limb surgeries.

Aims and objectives

Primary objective is to compare the duration of analgesia and pain scoring by visual analogue scale. The secondary objective is to monitor sedation, hemodynamic changes and side effects like nausea, vomiting, shivering, pruritus etc.

MATERIALS AND METHODS

A randomized double-blind study was carried out on 80 patients posted for lower limb orthopedic surgeries

in MKCG Medical College and Hospital Berhampur after obtaining approval from the Institutional Ethical Committee from August 2021 to July 2023. Patients contraindicated for regional anesthesia, allergy to local anesthetics, stenotic cardiac disease, psychiatric disease, respiratory distress, coagulation abnormalities, history of drug abuse, or spine deformities were excluded from the study. Patients were randomly divided into two equal groups of 40 each by computer-generated codes, i.e., group RF, received 10 mL of 0.2% ropivacaine with 25 mcg of fentanyl and group RN, received 10 mL of 0.2% ropivacaine with 2.5 mg of nalbuphine. The patients and the anesthetists administering the drugs and the person keeping the data were blinded about the study drugs.

Under strict aseptic conditions, lumbar epidural anesthesia was performed using an 18G Touhy needle with patients in a sitting position in L3-L4 interspace. Epidural catheter (20G) was advanced cephalad 3–5 cm into the epidural space. A test dose of 3 mL of 2% lignocaine with adrenaline was administered into the epidural space. Lumbar puncture was done in the L₃-L₄ intervertebral space using a 25G quincke's needle and after ensuring free flow of cerebrospinal fluid, 3 mL of 0.5% bupivacaine was heavily injected intrathecally. After 1½ h of surgery, epidural top-up was given by pre-filled syringes in a blinded manner to both groups. During the study period, patient's heart rate, mean arterial pressure (MAP), respiratory rate, and Visual Analog Score (VAS) were noted every 5 min for 30 min, every 30 min subsequently for the next 2 h, and 2 hrly up to 8 h after epidural dose. Side effects such as nausea, vomiting, respiratory depression, motor blockade (Bromage scale >1), deep sedation (Ramsay sedation score >3), shivering, and pruritus were noted. Patients were given rescue analgesic (injection diclofenac 75 mg IV infusion) whenever complained of pain or VAS score >4.

Sedation score

The level of sedation was assessed using the observer's assessment of alertness/sedation scale.

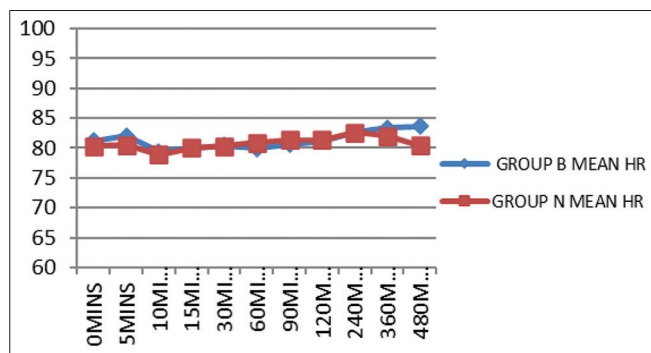
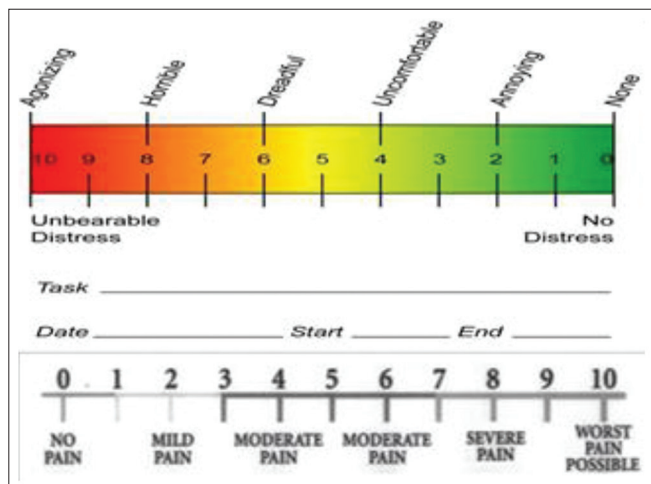
- Alert and wide awake
- Arousable to verbal commands
- Arousable to gentle tactile stimulation
- Arousable to vigorous shaking
- Unarousable.

Total duration of analgesia

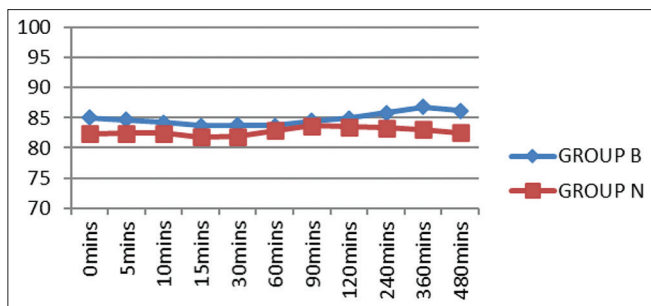
The time interval from the epidural top-up to the time when the patient complains of pain.

Time of first rescue analgesia

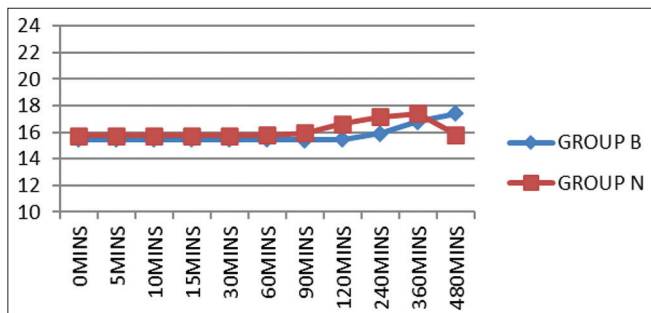
The time interval from the epidural top-up to the time the patient experiences the pain of VAS >4. Injection diclofenac sodium 75 mg IV infusion was given.



Graph 1: Mean heart rate comparison



Graph 2: Mean arterial pressure comparison



Graph 3: Comparison of respiratory rate

Parameters	Group RN	Group RF	P-value
Age (years)	35.80±11.074	35.03±10.927	0.596
Male (%)	22 (55)	18 (45)	0.371
Female (%)	18 (45)	22 (55)	
ASA I	34	35	0.745
ASA II	6	5	

	Group RN		Group RF		Statistical significance (P-value)
	Mean	SD	Mean	SD	
Mean duration of analgesia in minutes	398.45	62.245	222.88	51.382	0.0001

Pain score at 30 min	Group RN	Group RF
Good	38	37
Fair	2	3
Poor	0	0

Sedation score	Group RN	Group RF	Total
0	9	16	25
1	11	18	29
2	9	3	12
3	8	3	11
4	3	0	3
5	0	0	0
Total	40	40	80

Complication	Group RN		Group RF	
	Present	Absent	Present	Absent
Nausea and vomiting (%)	4 (10)	36 (90)	12 (30)	28 (70)
Pruritus	0	40	0	40

Statistical analysis

The collected data were entered into Microsoft Excel (MS-EXCEL, Microsoft Corp.) data sheet and analyzed with the statistical program the Statistical Package for the Social Sciences (IBM SPSS, version 17). Data were organized and presented using the principles of descriptive and inferential statistics. The data were categorized and expressed in proportions. The continuous data were expressed as mean±SD.

1. Two-sided independent Student *t*-test and Mann–Whitney *U*-test for parametric data
2. Chi-square test for non-parametric data.

P<0.05 was considered statistically significant.

RESULTS

Both the groups RN and RF were comparable in terms demographic profiles ie; Age, Sex, Weight and ASA grading (Table 1).

There was no statistically significant difference in mean heart rate from 0 minutes to 360 minutes between the groups RN and RF. Mean heart rate in group RN was 83.65/min and in group RF was 80.40/min at 480 minutes with p value 0.02 which is statistically significant. This may be due to onset of pain in nalbuphine group. The lower heart rate among participants of RF group at 480 minutes compared to those of RN group might be because of administration of rescue analgesia in RF group (Graph 1).

MAP were comparable from 0 to 240mins and were not statistically significant but p value of MAP in 360 and 480 mins was <0.05 which was statistically significant and this change in blood pressure might be due to onset of pain between 120 to 240mins in group RF and 360 to 480 mins in group RN (Graph 2).

There was no significant difference in the respiratory rates of both the groups during the initial 2 hrs, but there was significant rise in respiratory rate in both the groups, i.e. at 120 to 240mins in group RF and at 360 to 480 mins in group RN. This was due to discomfort from pain and loss of analgesic effect of drug. The rate came down to normal after rescue analgesia was given further confirming the assumption (Graph 3).

Table 2 shows that the mean duration of analgesia was 398.45 minutes in Group RN and 222.88 minutes in Group RF with a P value of 0.0001. The duration was thus significantly longer in nalbuphine group.

92.5% patients of group RF and 95% patients of group RN had good pain score on evaluation after 30minutes of administration of epidural drug which was not statistically significant. 7.25% and 5% had fair pain score respectively and no patients showed poor pain score. Hence both the drugs delivered a good amount of analgesia (Table 3).

Complications

Eleven patients (27.5%) in nalbuphine group and 3 patients (7.5%) in fentanyl group had sedation score of ≥ 3 . The majority of the patients had mild sedation; patients were awake but drowsy. This difference among the two groups was statistically significant (P value 0.018) Table 4.

In this study 10% of patients in Group RN and 30% patients in Group RF had nausea and vomiting, which was major side effect of fentanyl group. No patients

in nalbuphine group and fentanyl group had pruritus (Table 5).

DISCUSSION

Post-operative acute pain starts with the surgical trauma and usually ends with tissue healing. It diminishes with time after surgery and responds to analgesics. Severe pain can result in splinting with resultant atelectasis and hypoxemia. In addition, poor control of pain may result in increased catecholamine secretion which may in turn increase myocardial oxygen demand. A number of studies in the past have proved that improved post-operative analgesia may reduce the incidence of cardiac and pulmonary morbidity and mortality in patients undergoing lower limb surgery. In this study, an attempt was made to evaluate the duration of analgesia and the requirement of rescue analgesics after epidural administration of nalbuphine or fentanyl as adjuvant to 0.2% ropivacaine and to evaluate the side effects if any.

Kappa opioid receptors are mainly involved in the mediation of visceral pain. The use of epidural opioids has become an increasingly popular technique for the management of acute post-operative pain in recent times. However, disadvantages associated with narcotics are nausea and vomiting, pruritus, respiratory depression, and urinary retention. Stimulation of spinal opiate receptors (kappa, κ) can produce spinal analgesia but with fewer side effects. Nalbuphine hydrochloride is a mixed μ antagonist and κ agonist. It has been found to cause prolongation of the effects of local anesthetics in intrathecal, epidural, and peripheral nerve blocks with the advantages of minimal respiratory depression and better hemodynamic stability. Fentanyl is a synthetic μ receptor agonist. The high lipid solubility favors a shorter duration of action and greater systemic absorption. Diffusion of the drug into the epidural veins is the major route of clearance.

The mean pulse rate in Group RN and Group RF showed no significant change from 0 to 360 mins postop. Graph 1 showed that there was significant difference between the two groups at 360 to 480 mins with mean heart rate in group RN and group RF being 83.65 ± 4.870 and 80.40 ± 7.153 bpm respectively. It was mostly due to loss of analgesic effect of study drug and also regaining consciousness from sedation. The mean arterial blood pressure in both the groups was not significant for the first 240mins. The mean rise in MAP was statistically significant between both the groups from 240 to 480 mins which might be due to onset of pain at different intervals of time, the MAP of 86.35 ± 6.467 and 83.05 ± 5.167 mm of Hg at 360 mins for group RN and RF respectively. Similarly MAP at 480 mins was 86.15 ± 6.407 and 82.53 ± 5.119 for group

RN and RF; p values being 0.014 and 0.007 which was statistically significant (Graph 2). No significant difference was observed in the mean respiratory rate between the 2 groups for the first 4 hrs but later on p value was <0.05 at 240 to 480 mins due to decrease effect of epidural drugs. Oxygen saturation (SPO₂) maintained between 98-97% in both the groups (Graph 3).

The mean duration of analgesia in group RN and group RF was 398.45±62.245 and 222.88±51.382 mins respectively with p-value<0.05 i.e. statistically significant (Table 2 and 3). It showed nalbuphine group had longer pain free period as compared to fentanyl group. S Manojprabhakar, M Dhakshinamoorthy *et al.*¹⁰ found that epidural nalbuphine 10 mg with 0.125% bupivacaine provided longer duration of analgesia compared to 100 mcg fentanyl with 0.125% bupivacaine both diluted to 10 ml with normal saline was similar to our results. Hala Mostafa Gomaa *et al.*¹¹ found that an intrathecal adjuvant of nalbuphine 0.8mg to hyperbaric bupivacaine for cesarean delivery intensified postoperative analgesia more as compared to fentanyl 25µgm and hyperbaric bupivacaine mixture and this was in line with our observations. In a 2017 Swarna Banerjee *et al.*¹² concluded that addition of nalbuphine 10 mg to 0.125% hyperbaric bupivacaine prolonged duration of postop analgesia compared to 100mcg fentanyl with 0.125% bupivacaine which was consistent with our study. Veena Chatrath *et al.*¹³ in 2015 found that 10mg nalbuphine as epidural adjuvant to 0.25% bupivacaine has significant longer duration of analgesia compared to 100mg tramadol. Oinam Bisu Singh *et al.*¹⁴ demonstrated that nalbuphine as epidural adjuvant to ropivacaine had prolonged duration of postoperative analgesia for more than 6 hours. Babu S *et al.*¹⁵ found that addition of nalbuphine as epidural adjuvant to ropivacaine prolonged the duration of analgesia by more than 6 hours. The above observations were similar to our study results.

The major side effects of nalbuphine was sedation with 27.5% patients of group RN as compared to 7.5% patients of group RF. Whereas nausea and vomiting is one of the major drawbacks of fentanyl seen in 12% & 4 % patients of group RF and group RN respectively (Table 4 and 5). Pruritus and respiratory depression was not seen in any of the groups.

Limitations of the study

1. Small sample sizes might compromise the generalizability of the study. Hence, we recommend a large randomized controlled trial to confirm this evidence
2. Different concentrations of adjuvants could have been tried with multiple top-up doses
3. It could have been tried with other epidural techniques

such as thoracic epidural and sacral epidural with different surgeries.

CONCLUSION

It was concluded that epidural nalbuphine in a dose of 2.5 mg with 0.2% ropivacaine provided a longer duration of analgesia with better pain score and more sedation which was advantageous for post-operative patient compliance and satisfaction as compared to 25 mcg of fentanyl with 0.2% ropivacaine.

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Authors Contribution:

AKH- Literature survey, preparation of the manuscript, implementation of the study protocol, and data collection; **BPS**- Concept, design, clinical protocol, manuscript editing, and revision; **SJ**- Manuscript writing, statistical analysis, and interpretation; **HD**- Literature survey and preparation of tables, manuscript revision, and editing; **SD and DB**- Design of study, ethical approval, and data collection; **MK**- Manuscript preparation, literature review, protocol preparation, and implementation of the study.

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