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Research Article

Comparative Efficacy of 2mg and 5mg Intrathecal Nalbuphine as an Adjuvant to Ropivacaine in Elective Lower Limb Surgeries

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ABSTRACT
Background: Spinal opioids can provide profound analgesia with fewer central and systemic adverse effects than with opioids administered systematically. In this prospective, randomised, double-blind study, we compared the efficacy of 2 mg and 5 mg intrathecal Nalbuphine as an adjuvant to Ropivacaine in elective lower limb surgeries.
Materials and Methods: 90 patients aged 18-60 years, ASA grade I and II, undergoing elective lower limb surgery were randomly divided into two groups. Groups A and B, who received 2 mg and 5 mg nalbuphine, made up to 0.5 mL volume with normal saline, added to 3ml of isobaric 0.75% ropivacaine, (total volume of 3.5 mL) respectively. The hemodynamic parameters following administration of the drug, onset of sensory block, onset of motor block, duration of motor block, two-segment regression time of sensory block, quality of analgesia, duration of analgesia, and the incidence of adverse effects were compared between the groups.
Results: The onset of both sensory and motor blockade was faster with the addition of 2 mg and 5 mg of nalbuphine with ropivacaine; however, it was not statistically significant ($P > 0.05$). Two-segment regression time and duration of analgesia and motor blockade, the duration of sensory blockade, VAS readings, and haemodynamic variability were comparable between the two groups. Incidence of adverse effects were more in group B which is statistically significant difference ($P<0.05$).
Conclusion: It was found that when compared with 5 mg of nalbuphine, 2mg nalbuphine is equally good as an adjuvant to isobaric 0.75% ropivacaine in elective lower limb surgeries with prolonged analgesia, a reliable block with equal efficacy but with fewer side effects.

Keywords: Intrathecal Nalbuphine, Postoperative Analgesia, Isobaric Ropivacaine.

INTRODUCTION

Spinal Anaesthesia is the widely used method for lower limb Orthopaedic surgeries, providing a faster onset and effective motor and sensory blockade. It is simple, easy to perform and has a definite endpoint. Intrathecal bupivacaine is widely used in spinal anaesthesia over a long period of time. Ropivacaine has emerged, which is being widely used for epidural blocks and nerve plexus blocks. Nowadays, ropivacaine is gaining increasing popularity because of reduced risk of central nervous system and cardiac toxicity, early ambulation and discharge with good quality of postoperative analgesia.[1] Though ropivacaine is being used frequently, in epidural and nerve blocks, the literature regarding its use in intrathecal route is sparse. Various adjuvants have since been added to local anaesthetics to increase the quality and duration of spinal blockade as well as prolong

postoperative analgesia. Different adjuncts such as alpha-2 agonist clonidine and dexmedetomidine, neostigmine, midazolam, ketamine, epinephrine, magnesium sulphate, and butorphanol were used previously with local anaesthesia [2,3]. Intrathecal opioids reduce the release of gamma-aminobutyric acid and glycine by a calcium-independent process from dorsal horn neurons.[4] Nalbuphine is a mixed opioid agonist–antagonist which can prove to be particularly advantageous because of the potential to maintain or even enhance opioid-based analgesia while simultaneously eliminating the common μ-opioid side effects (nausea, emesis, pruritis, constipation, undesirable sedation, respiratory depression and the development of tolerance/dependence).[5,6] Our study aims to find out the optimum dose of nalbuphine as an adjuvant to ropivacaine to produce significant prolongation in the duration of analgesia without adverse effects.

MATERIALS AND METHODS

After obtaining approval from the institutional ethical committee (VIREC no:19270/Dt.20.02.20/IST-216/19), the study was prospectively registered with Clinical Trials Registry (registration no: CTRI/2021/01/030645). This double-blind randomized controlled clinical study was conducted on 90 patients scheduled for elective lower limb orthopedic procedures under subarachnoid block after obtaining the informed consent. Patients of 18–60 years of age, both male and female, 40-90 kg body weight American Society of Anaesthesiologists (ASA) I and II physical status were included in this study. Patients with a history of allergy to the study drugs, pregnant patients, history of psychiatric illness, history of comorbidities, coagulopathy, local infection at injection site and any spinal deformity were excluded from the study. Patients were randomly allocated to two groups by computer-generated randomization: Each group consists of 45 patients. They received either of drug solution as below.

- **GROUP A (n=45)**: received 2mg nalbuphine made up to 0.5ml volume with normal saline plus isobaric ropivacaine 0.75% 3ml (Total volume 3.5ml)
- **GROUP B (n=45):** received 5mg nalbuphine made up to 0.5ml volume with normal saline plus isobaric ropivacaine 0.75% 3ml (Total volume 3.5ml)

The study drug was injected by an independent anaesthesiologist in a double-blind fashion who did not participate in observation or collection of data. Both the patient and the anaesthesiologist were blinded to the patient's group assignment and all recordings were performed by an anaesthesiologist, who was blinded to the randomization schedule.

Preanesthetic evaluation was done to all patients under inclusion criteria Basic laboratory investigations were done. The entire procedure of spinal anesthesia was explained to the patient. Patients were explained about visual analogue scale (VAS) and were taught how to express the degree of pain on the scale. Premedicated with tab diazepam 10 mg and tab ranitidine 150 mg orally night before surgery and were kept nil per orally for 8 hours before surgery.

In the operating room, routine monitors like Noninvasive blood pressure, pulseoximetry, Electrocardiogram were connected. Before administration of Subarachnoid block, vital parameters were recorded. Patients received intravenous pre-hydration with 10 mL/kg Ringer lactate. Under aseptic precaution, lumbar puncture performed in the L3-4 interspace with 25 G Quincke's spinal needle in the sitting position. The patient received either one of the drug solutions as per allocated group and made to lie supine. Intra-operative fluid requirements given as necessary depending on the blood loss and hemodynamic parameters. Any incidence of Hypotension, defined by a Mean arterial pressure < 65mm of Hg, was noted and treated with inj. Ephedrine 6 mg iv boluses. Any incidence of Bradycardia, defined by a heart rate of <60 bpm, was noted and treated with inj. Atropine 0.6 mg iv bolus. In case of any respiratory depression oxygen is administered through face mask at rate of 4L/min. Incidence of nausea, vomiting and pruritus was noted.

The following parameters were noted and used for comparison between the groups: a) The onset of sensory blockade (time taken from the end of injection to by Hollmen Scale score 4 at T10 dermatome), b) complete motor blockade (time taken from the end of injection to development of modified Bromage's grade 3 motor block), c) highest level of sensory blockade, d) Hypotension, bradycardia, and respiratory depression.e) duration of sensory blockade (two-segment regression time from highest level of sensory blockade), f) duration of motor blockade (time required for motor blockade return to Bromage's grade 0 from the

time of onset of motor blockade), g) duration of effective analgesia (time from the intrathecal injection to the first analgesic requirement, VAS score 3 or more), h) incidence of side effects like nausea, vomiting, urinary retention, and itching.

Patients reporting a VAS score 3 or more received rescue analgesics in the form of injection Inj. diclofenac 75 mg i.v. Nausea and vomiting were treated with Inj. ondansetron 4 mg i.v. and pruritus with anti-histaminics.

Vitals were recorded at 0, 2, 5, 10, 15 and 30 min and then at every 15 min intervals intraoperatively and postoperatively for 2 h, later at 4th, 8th, 12th, 16th, and 24th h. Both sensory and motor block were assessed at 2,4 and 5 min, and then at 5-min intervals for first 30 min. Assessment was continued at 30-min intervals following the completion of surgery till till normal motor function returned. The sensory block was assessed bilaterally along the mid-axillary line using a short beveled 20-G hypodermic needle evaluated by Hollmen Scale (Score 1 = Normal sensation of pinprick. Score 2 = Pin prick felt as sharp pointed but weaker compared with same area in the other upper limb. Score 3 = Pin prick recognized as touch with blunt object. Score 4 = No perception of pin prick). The motor block was assessed using the modified Bromage scale (0 = full movement, 1 = unable to raise extended leg, 2 = unable to flex knee, 3 = no movement). The intensity of pain was assessed by VAS (no pain at 0 to maximum pain at 10 point) at 0, 10, 15, 30 and 60 min and then at 30-min intervals.

Statistical Analysis

Based on previous studies [7], it was calculated that a sample size of 25 patients would be required per group to demonstrate a clinically significant difference among the groups. Calculations were done using sample-size.net. For better results, we included 45 subjects in each group.

The statistical analysis was done using Statistical Package for Social Science evaluation (SPSS) version 23. Results are expressed as mean, standard deviation, and range. Quantitative data was analysed using the independent student t-test, and presented as mean and standard deviation. Categorical data was analysed using the chi-square test, and presented as percentages. A p value of <0.05 was considered statistically significant.

RESULTS

Ninety patients were enrolled in this study by dividing them into two groups of 45 each. Both the groups were comparable in all demographic data such as age, sex, weight, height, ASA grade and duration of surgery (Table 1); $P > 0.05$. The onset of sensory and motor block was found to be statistically insignificant ($P > 0.05$) in both the groups. Two-segment regression time, duration of motor blockade and duration of effective analgesia were comparable ($P > 0.05$) in both the groups [Table 2]. In both the groups the higher sensory block was achieved between T6 and T8. Both the groups did not vary significantly in terms of intraoperative mean heart rate, systolic and diastolic blood pressure, mean arterial pressure, respiratory rate and SPO2 [Figure 1,2,3]. There was statistically significant difference (P<0.05) in nausea, vomiting, and pruritus between the two groups. [Figure 4].

Table No-1: Demographic Data in Both the Groups

	Group A (n=45)	Group B(n=45)	P value
Age in years (Mean±SD)	40.71±13.19	40.02±12.11	0.797
Sex(M:F)	27:18	25:20	0.670
Weight in kg (Mean±SD)	57.04±5.334	58.68±5.857	0.167
Height in cm (Mean±SD)	162.28±6.73	162.57±7.782	0.851
ASA (I:II)	20:10	18:12	0.592
Duration of Surgery(mins)	191.84±19.5	185.88±5.19.67	0.153

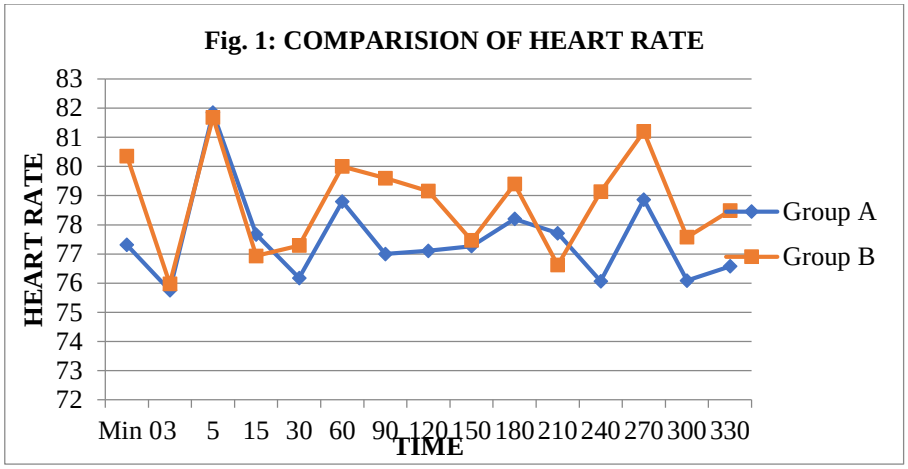

Fig 1: Comparison of Heart Rate in Both the Groups ($P > 0.05$)

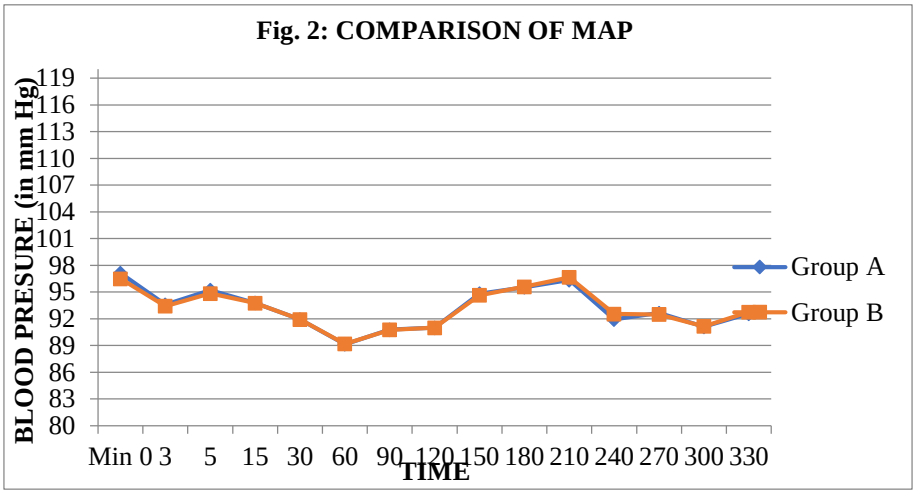

Fig 2: Comparison of MAP in Both the Groups ($P > 0.05$)

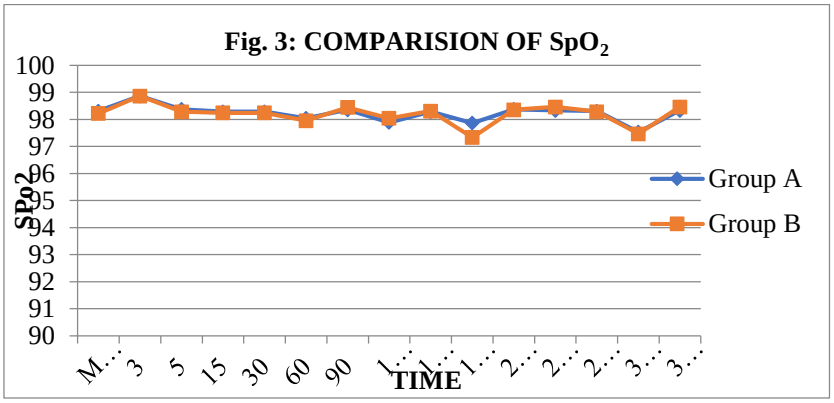

Fig 3: Comparison of Spo2 in Both the Groups ($P > 0.05$)

Table 2: Sensory Block, Motor Block and Analgesia in Both the Groups

	Group A (Mean ± SD)	Group B (Mean ± SD)	p value
Time for onset of Sensory Block(min)	3.93±0.64	3.89±0.57	0.807
Peak sensory level (thoracic)	6.93 ±1.38	6.89±1.56	0.887
Time for Complete Motor Block(min)	8.44±0.893	8.48±0.895	0.814
Two segment sensory regression time(min)	118.32±32.64	119.41±2.87	0.448

Total Duration of Motor Block(min)	225.33±13.29	223.2±13.31	0.449
Duration of Analgesia(min)	242.62±13.07	241.91±12.37	0.792

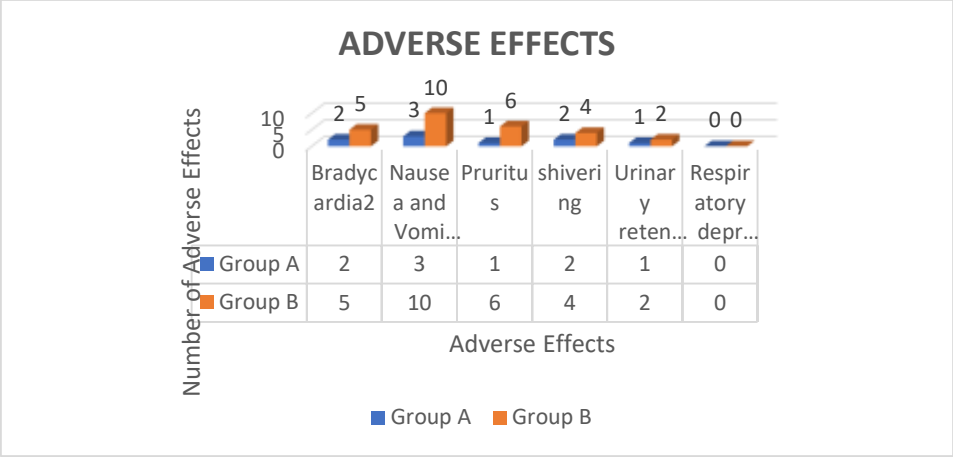

Fig 4: Frequency of Adverse Effects in Each Group

DISCUSSION

Spinal opioids can provide profound analgesia with fewer central and systemic adverse effects than with opioids administered systematically.[8] The technique of intrathecal opioid administration along with local anaesthetics has been studied extensively and found to provide superior quality of analgesia in a variety of surgical procedures.[9.10] The rationale for the combination of opioids and local anaesthetics is that these two types of drugs eliminate pain by acting at two different sites. Local anaesthetics act at the nerve axon, whereas opioids act at the receptor site in the spinal cord.[11] Intrathecal opioids used as adjuncts also allow early ambulation of patients because of their sympathetic and motor nerve sparing activities.[12] The most commonly used intrathecal opioids are mu agonist drugs that provide excellent analgesia and also carry along with them various mu-mediated side effects. Nalbuphine is a mixed agonist–antagonist opioid which has agonistic activity at the kappa receptors providing good intraoperative and postoperative analgesia and has antagonistic activity at the mu receptors, thereby exhibiting less mu-mediated side effects.[13]

We used isobaric 0.75% ropivacaine with two different doses of nalbuphine in our study as it blocks sensory nerve fibers more readily than motor fibers thus helping early ambulation and is now gaining popularity due to its reduced cardiac toxicity with overdose.[14] In our study, we tried to find the most optimal dose among the two groups of nalbuphine as an adjuvant to ropivacaine which can provide adequate analgesia with minimal side effects in elective lower limb surgeries. Very few studies have been done comparing different doses of intrathecal nalbuphine as an adjuvant with isobaric ropivacaine. Most studies have found intrathecal nalbuphine to produce a significant analgesia accompanied by minimal pruritus and respiratory depression.[15]

Nalbuphine does not exacerbate the sympathetic blockade caused by ropivacaine, keeping the incidence of intraoperative bradycardia and hypotension low and comparable across both groups. [13]. Both 2mg and 5mg doses maintain excellent perioperative hemodynamic stability. Similar findings are seen in the study conducted by Culebras *et al.*,[16] Tiwari *et al.*,[17] where there were no gross hemodynamic changes throughout their study. From our study, we can conclude that use of nalbuphine hydrochloride along with Ropivacaine causes no gross hemodynamic disturbances even with increasing the dosage from 2 to 5 mg.

Various animal studies have also been conducted to confirm that nalbuphine is not neurotoxic. Rawal *et al.* in a sheep model showed that even large doses of 15–24 mg of napbuphine were not associated with hypertensive changes in spinal cord or any behavioural or systematic histopathologic abnormalities.[18] Nalbuphine is being used intrathecally for more than 10 years now without any adverse neurotoxic effects.

The onset time of both sensory and motor blocks is less in group B than group A (3.93±0.64, 3.89±0.57 min respectively). However, they were not statistically significant ($P > 0.05$). Two-segment regression time,

duration of analgesia and duration of motor blockade were comparable in both the groups ($P > 0.05$). Both the groups had comparable VAS readings. All the groups were statistically comparable in terms of adverse effects although the group B had slightly higher incidence of adverse effect. Jyothi *et al*. [19] have used up to 2.5 mg of nalbuphine, Gupta *et al*. [20] have compared nalbuphine (2 mg) versus fentanyl (25 mg) as a supplement to 0.5% bupivacaine (3.5 ml) and adjudged that nalbuphine produced more duration of analgesia, motor block without any adverse effects.

Although the incidences of adverse effects were more in group B, it was clinically and statistically insignificant. In our study, none of patient had respiratory depression (respiratory rate below 10 per minute, SPO2 <90%). Nalbuphine exhibits ceiling effect for respiratory depression. This is proved in studies done by Romagnoli and Keats[21]. Since respiratory depression is predominantly μ receptor mediated and nalbuphine is a μ receptor antagonist, respiratory depression effect is expected to be attenuated by nalbuphine. Increasing the dosage from 2 to 5mg did not cause any respiratory complications. This result correlates that of the studies done by Culebras *et al*.,[16] and Tiwari *et al*.,[17]. Since nalbuphine reaches ceiling effect at lower intrathecal dosage, the increased drug dosage is not required and this increases the safety margin.

LIMITATIONS

Main limitation of our study is that we have not added a placebo group in our study despite choosing appropriate doses of nalbuphine for comparison after careful analysis of previous studies. We avoided a placebo because of ethical concerns and believe that it would not have produced a major impact on the study.

CONCLUSION

Intrathecal nalbuphine can be a good adjuvant to subarachnoid block as it can prolong both sensory and motor blockade with minimal side effects. Both 2 and 5 mg nalbuphine can be used safely intrathecally with isobaric 0.75% ropivacaine in elective lower limb surgery as they both provide prolonged analgesia and a reliable motor block with equal efficacy but 2mg nalbuphine with 0.75% ropivacaine provides analgesia with lesser side effects.

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