INTRATHECAL NALBUPHINE VS. BUPRENORPHINE AS AN ADJUVANT TO ROPIVACAINE 0.75% HEAVY IN LOWER LIMB ORTHOPAEDIC SURGERIES: A PROSPECTIVE RANDOMIZED CONTROLLED STUDY.

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Abstract:

Background and Aims: Subarachnoid block for the lower limbs is a safe and reliable technique. The present study aimed to compare intrathecal nalbuphine and buprenorphine as adjuvants to ropivacaine 0.75% heavy in lower limb orthopaedic surgeries.

Methods: Sixty patients admitted to the hospital during the study period and met the inclusion criteria were recruited and randomized either to nalbuphine group (Group N, n=30) and buprenorphine group (Group B, n=30). Group N: 22.5 mg 0.75% hyperbaric Ropivacaine (3.0 ml) + 1 mg Nalbuphine (0.5 ml) and Group B: 22.5mg 0.75% hyperbaric Ropivacaine (3.0 ml) + 60µg Buprenorphine (0.5 ml). Sensory block onset, sensory block regression, motor block onset, motor block regression, rescue time and blood pressure were evaluated and compared. Chi-square test and independent t-test were used for statistical analysis.

Results: Sensory block onset, sensory block regression, motor block onset, motor block regression and time to first rescue analgesic were significantly shorter ($p<0.001$) in Group N than in Group B. The fall of BP from baseline was significantly more in group B compared to group N($p< .01$). Hypotension was seen in 2 patients in Group B only but which resolved with IV fluids.

Conclusion: When used as adjuvants to ropivacaine intrathecally, nalbuphine showed a faster onset time for both sensory and motor block though the time to first rescue analgesic was significantly longer with buprenorphine in lower limb orthopaedic surgeries.

Keywords: Ropivacaine, buprenorphine, nalbuphine, analgesia, anaesthesia,

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INTRODUCTION

For a long time the armamentarium of anaesthesia relied upon the giant shoulders of general anaesthesia and central neuraxial blockade. The choice between these two depends upon the surgery demand and physical status of the patient.

As the name implies, regional anaesthesia only affects the area of the body that will be used for the surgical procedure. Because to its advantages over general anaesthesia, a well-executed regional anaesthetic approach has a lot to offer the anaesthesiologist, surgeon, and patients. Immunocompetence is less affected, polypharmacy is avoided, better hemodynamic stability is provided, excellent postoperative analgesia is provided all of which contribute to a shorter hospital stay. Subarachnoid block regional anaesthesia for the lower limbs is an easy, secure, and reliable technique. [1,2]

In order to extend the time of postoperative analgesia after lower limb procedures, a number of medications have been tested, including opioids, alpha 2 agonists, midazolam, and dexamethasone. Nalbuphine, which is a mixed kappa and mu antagonist analgesic, is basically a derivative of 14-hydroxymorphine. It has a lesser incidence of postoperative complications like nausea, vomiting, and pruritus and can produce strong analgesia and hemodynamic stability. Nalbuphine's activation of kappa receptors, which prevents the production of pain-related neurotransmitters such substance P, may contribute to the prolongation of the anaesthetic effect and analgesia. [2-4]

Buprenorphine, which is a delta receptor antagonist as well as mu and kappa receptors agonist, is basically a derivative of thebaine and capable of producing prolonged analgesia. In comparison to morphine, buprenorphine has a mu receptor affinity that is 50 times higher, and this gradual dissociation from these receptors is what gives buprenorphine its extended duration of action. Its advantages are sedation, affordability and the absence of harmful side effects including respiratory depression. [5-6]
The present study was conducted to compare intrathecal nalbuphine and buprenorphine as adjuvants to ropivacaine 0.75% heavy in lower limb orthopaedic surgeries as limited data are available to compare the two adjuvants with ropivacaine.

MATERIALS AND METHODS:

Sampling

With the approval of Institutional Ethics Committee (MGMC&H/IEC/JOR/2022/680), the single-centered, double-blinded, prospective randomized controlled study was conducted. This study has also been registered in the Clinical Trial Registry of India (CTRI/2023/02/049395). Informed consent was obtained from all the patients. The sample size calculation was done using G*Power software; considering 80% power of the study and 5% alpha error, the total sample size was 60.

Sixty patients of either sex and aged between 18–60 years, admitted to the hospital during the study period and met the inclusion criteria were recruited. As per American Society of Anaesthesiologist physical status I and II, patients scheduled to undergo lower limb orthopaedic surgery under intrathecal anaesthesia were considered for the study. The patients with American Society of Anaesthesiologist physical status III and IV status, with gross spinal deformity, local infection, neurological diseases, bleeding disorder, cardio-respiratory diseases, liver diseases, chronic users of narcotics, sedatives, and drug abusers or alcoholics and those allergic to any of the medications used in the study, were excluded. Using a computer generated random number table, patients were randomly allocated to two groups each comprising of 30 patients. Allocated groups were Group N: 22.5 mg 0.75% hyperbaric Ropivacaine (3.0 ml) + 1 mg Nalbuphine (0.5 ml) and Group B: 22.5mg 0.75% hyperbaric Ropivacaine (3.0 ml) + 60µg Buprenorphine (0.5 ml). These drugs were premixed in a sterile technique by the principal investigator. Triple blinding was done that is the patient, the anaesthetist performing the sub arachnoid block and the evaluator had no knowledge about the drug which was administered.

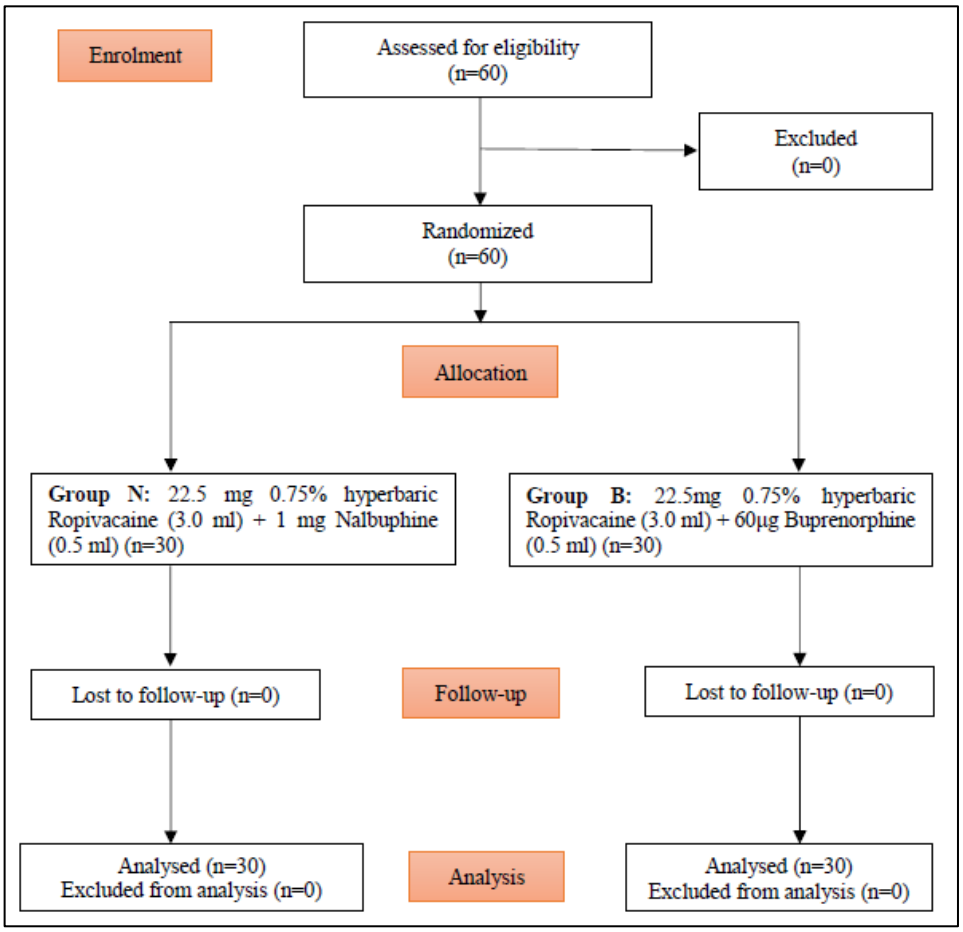


Figure 1: Consort flow diagram

Methodology

After doing all the required investigation, PAC was be performed a day before the surgery. Patients were shifted to the operating table and monitors were attached and the baseline values of the following parameters were noted: Heart Rate, Blood Pressure (systolic, diastolic, and mean), Peripheral oxygen saturation (SpO2) and Electrocardiograph.

A wide bore intravenous access was secured using an 18 G intravenous cannula and co-loading was done with 15 ml/kg of Ringer's lactate infused intravenously. Subarachnoid block was performed under strict aseptic precautions, with patient in sitting position and through mid-line approach, a 25 G Quincke's needle was inserted into subarachnoid space at the level of L3-L4 or L4-L5 interspinous space till the loss of resistance was felt and free flow of CSF was confirmed at the hub of the spinal needle. Then 3.5 ml of study drug solution was injected intrathecally slowly over 10 seconds with the bevel facing cephalad. The time of drug injection was noted and all the observations were made using this time as '0' minute. Immediately, the patient was placed in supine position and oxygen was administered by face mask. Ringer's lactate solution was used for maintenance and replacement of blood loss (till allowable limit). For in-correctable hypotension (defined as decrease in systolic BP by more than 20% from baseline) treated with IV fluids, vasopressor will be used that is Inj Mepehentermine titrated between 5-30mg according to response and for decrease in heart rate (<40/min) inj Atropine 0.6mg will be used .

Sensory parameters were observed and recorded intraoperatively and postoperatively. The time taken for the block to reach T10 segment was taken as onset of sensory block. The time taken to highest level of block was noted as the time from intrathecal injection to the highest sensory level achieved. Time taken for two-segment regression of sensory level was taken as the duration of sensory block.

Motor block was assessed by using the Modified Bromage Scale (0–3). Onset of motor block was taken as Modified Bromage grade 3. Systolic and diastolic blood pressure were recorded every 10 min for the entire intraoperative period and every 1 h postoperatively till complete recovery.

In the current study visual analogue scale (VAS) grading was recorded every 15min for the first 1

hour and subsequently for every hour for the next 8 hour after completion of surgery. VAS scale was used for the provision of giving rescue analgesia (IV Tramadol 100mg) whenever the VAS score was >4 and the time for rescue analgesia that is time from intrathecal injection to the first request of analgesia was also recorded

Statistical analysis

Statistical analysis was performed by using SPSS software (SPSS Inc., Chicago, IL, USA, version 16). Data were tabulated in Microsoft excel (Microsoft office 2019, Redmond, WA, USA) and presented with mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Chi-square test and independent t-test were used. A value of $P < 0.05$ was considered statistically significant.

RESULTS:

Table 1 shows the comparison of mean arterial pressures at baseline, just before SAB, at the end, 10 minutes, 20 minutes, 30 minutes, 1 hour, 1 hour 30 minutes and 2 hours. The mean arterial pressures were significantly lower in group B compared to group N at 10 minutes ($p<0.01$), 20 minutes ($p=0.02$), 30 minutes ($p<0.01$), 1 hour ($p<0.01$) and 1 hour 30 minutes ($p<0.01$)

Table 2 shows the differences of block characteristics between the groups. Sensory and motor block onsets were significantly shorter ($p<0.001$) in Group N. Sensory block regression, motor block regression and rescue time were significantly longer ($p<0.001$) in Group B. Hypotension was seen only in 2 patients in Group B which was absent in Group N but for which no intervention was required

In the Nalbuphine group, the patients achieved VAS score ≥4 on or before 6 hours and in the Buprenorphine group, the pa patients achieved VAS score ≥4 on or after 7 hours. Majority of the patients in Nalbuphine group achieved VAS score ≥4 on 5 hours 30 minutes (73.3%) and majority of the patients in Buprenorphine group achieved VAS score ≥4 on 7 hours 30 minutes (70.0%) (Table 3).

Both groups had minimal side effects. No post operative nausea, vomiting, pruritus, respiratory depression, euphoria dysphoria, desaturation was observed in both groups.

Table 1: Comparison of MAP at different time intervals

MAP	Group N (n=30)	Group B (n=30)	p value
Baseline	98.9±9.97	97.19±8.98	0.41
Just before SAB	98.74±9.5	93.98±10.19	0.18
At the end	89.96±10.97	86.46±8.51	0.11
10 minutes	86.56±9.23	79.80±10.93	<0.01
20 minutes	86.57±10.31	81.16±8.56	0.02
30 minutes	86.03±8.30	79.16±7.04	<0.01
1 hour	83.76±8.15	82.21±6.37	<0.01
1 hour 30 minutes	86.10±6.99	81.17±5.28	<0.01
2 hours	83.72±8.80	82.19±5.12	0.59

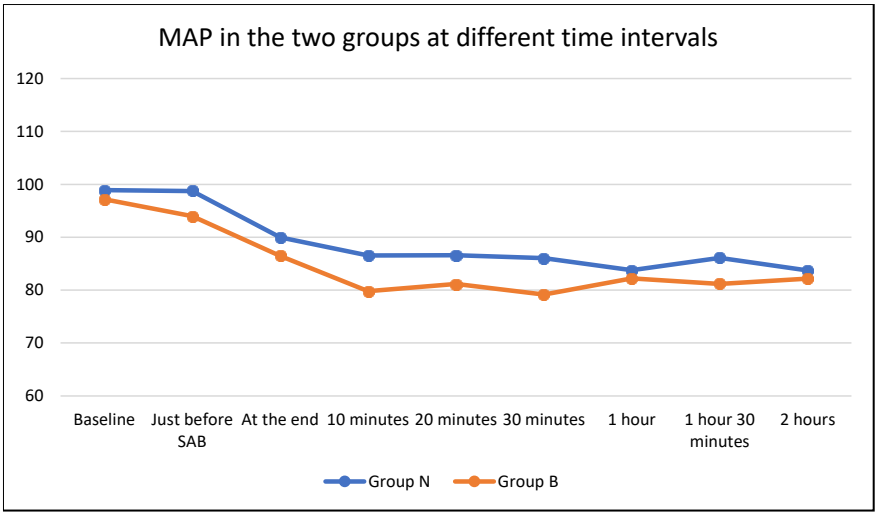
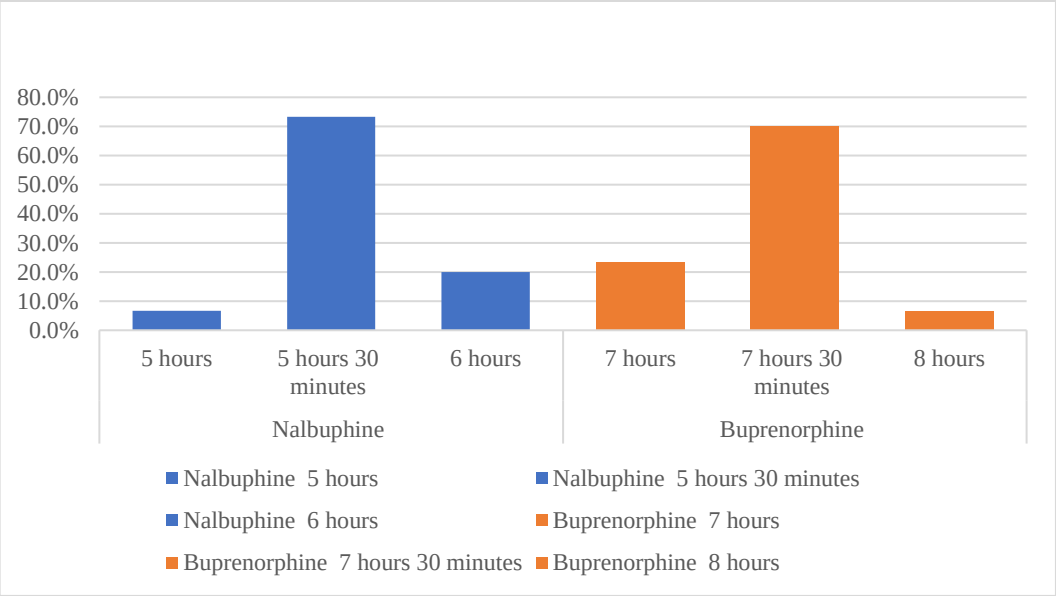


Table 2: Sensory and motor block in both groups at different interval

Parameters	Group N (n=30)	Group B (n=30)	p value
Sensory block onset (seconds)	104.87±37.32	178.8±40.18	<0.001
Sensory block regression (minutes)	185.20±13.69	242.37±12.49	<0.001
Motor block onset (seconds)	144.43±37.24	228.07±48.98	<0.001
Motor block regression (minutes)	170.3±15.20	192.63±12.96	<0.001
Rescue (minutes)	339.03±16.39	454.23±11.79	<0.001

Table 3: Distribution of patients achieving VAS score ≥4 at different time intervals

Group	Time	n	%
Nalbuphine	5 hours	2	6.7%
	5 hours 30 minutes	22	73.3%
	6 hours	6	20.0%
Buprenorphine	7 hours	7	23.3%
	7 hours 30 minutes	21	70.0%
	8 hours	2	6.7%



DISCUSSION:

The present study was conducted to evaluate and compare the anaesthetic and analgesic effects of intrathecal nalbuphine and buprenorphine as adjuvants to ropivacaine 0.75% heavy during the orthopaedic surgeries involving the lower limbs. There were no significant differences in terms of age, sex or weight between the nalbuphine and buprenorphine groups, and these findings were similar to the studies by Prabhu et al. and Naaz et al. [7,8]

Sensory block onset and motor block onset were significantly shorter (p<0.001) in nalbuphine group than in buprenorphine group. Sheth et al. reported similar outcomes where the buprenorphine group received 15 mg of 0.5% hyperbaric Bupivacaine with 60 µg of buprenorphine and the nalbuphine group received 15 mg of 0.5% hyperbaric Bupivacaine with 0.8 mg nalbuphine.[10] This is contradictory to the research done by Manjula et al., which found that the onset of sensory and motor block was nearly identical in the nalbuphine group under 3ml of 0.5% (H) Bupivacaine (15mg) + 0.8mg (0.1ml) of Nalbuphine and buprenorphine groups under 3ml of 0.5% (H) Bupivacaine (15 mg) + 0.5ml (60µg) of buprenorphine.[9] Prabhu et al. reported a different result that was, Sensory block onset was significantly shorter in nalbuphine group who were given Inj Bupivacaine (0.5%) 15mg + Inj Nalbuphine 0.8 mg (1 ml) but motor block onset was significantly shorter (p<0.001) in buprenorphine group who were given Inj Bupivacaine (0.5%) 15 mg + Inj Buprenorphine 60 microgm(1 ml). They also reported that, the duration of sensory and motor blocks were significantly shorter in nalbuphine group than in buprenorphine group which is in accordance with

the present study.[7] On the other hand Tiwari et al. found that sensory block onset, motor block onset and duration of motor block were shorter in nalbuphine group than in buprenorphine group but the differences were not statistically significant. [11] Buprenorphine has a quicker and longer-lasting impact because of its high lipid solubility, which allows it to penetrate lipid membranes more quickly and bind to receptors quickly and persistently, hastening the block. [12,13]

In comparison to nalbuphine, the use of buprenorphine considerably extended the time of postoperative analgesia. As a result, compared to the nalbuphine group, the duration of rescue analgesia was also longer in the buprenorphine group. These outcomes were akin to those reported by Manjula et al. who found that adding buprenorphine considerably lengthened the duration of postoperative analgesia. [9] Kaushal et al. also reported that, Time for first dose of rescue analgesia was prolonged in buprenorphine group compared to nalbuphine group. [14] Singh et al. showed that addition of buprenorphine to ropivacaine results in longer duration of analgesia. [15] Pratap et al. showed that, duration of effective analgesia and time for rescue analgesia were significantly longer in buprenorphine group than in nalbuphine group. [16] The long-lasting analgesia produced by the buprenorphine group is possibly a result of its high affinity and binding capability for mu receptors. It exhibits gradual detachment from its receptors. Because of its intense lipophilicity, it has a low plasma concentration, which further extends the duration. [17]

In the buprenorphine and nalbuphine groups, there was a significant difference in mean BP in terms of hemodynamic parameters. The systolic and diastolic blood pressures remained near baseline in nalbuphine group than in buprenorphine group. Similar findings were shown by Sheth et al. who found that nalbuphine had no hemodynamic instabilities or variations when compared to buprenorphine [10] . Manjula et al. and Tiwari et al. reported no significant difference was found in various haemodynamic vital parameters intra operatively between the two groups. [9,11] Kaushal et al. reported a result which was contradictory to the present study. They found that, higher blood pressure and heart rate were seen in the buprenorphine group than in nalbuphine group. They explained that, this can be due to nalbuphine's strong affinity for kappa opioid receptors, which also helps to stabilise the heart rate and provide sedation, analgesia, and little respiratory depression. [14] Buprenorphine exhibits analgesic property both at spinal and supraspinal levels and as it is highly lipid soluble and diffuses quickly into neural tissue it decreases the chances of rostral spread leading to lesser side effects in the post-operative period. [18,19]

No significant side effects were found in nalbuphine group whereas 2 patients in buprenorphine group showed hypotension. This is supported by various studies. [9,11,15,16] Although Kumari et al. reported a few incidences of hypotension, bradycardia and nausea in the nalbuphine group. [20]

CONCLUSION:

From the results of the present study, we can conclude that, when used as adjuvants to ropivacaine intrathecally, buprenorphine produces prolonged postoperative analgesia in lower limb orthopaedic surgeries. As the current study was done taking ropivacaine as our base drug, there are very few studies have been conducted using ropivacaine and comparing two adjuvants. Also this study was conducted only among the patients undergoing surgeries in their lower limbs, further research work involving surgeries in different other organs and using lower doses of the drugs are recommended.

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