

Duration of postoperative analgesia with Nalbuphine vs Butorphanol as an adjunct to spinal anesthesia for lower limb orthopedic surgeries: A randomized double-blind active control trial

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Abstract

Background and Aims: Nalbuphine as well as butorphanol as adjuvant to intrathecal bupivacaine have been studied in comparison to bupivacaine alone. Both are kappa receptor agonist and have never been compared for its efficacy in terms of postoperative analgesia. The aim of this study was to evaluate duration of postoperative analgesia as well as intraoperative block characteristics using intrathecal nalbuphine hydrochloride (800 µg) or butorphanol (25 µg) as adjuvant to hyperbaric bupivacaine (12.5 mg) in lower limb fracture femur surgeries as compared to active control, that is, saline and bupivacaine.

Material and Methods: This prospective, randomized, double-blind, active control study was conducted on 90 adult patients of either sex belonging to ASA grade I/II, aged 18–70 years, being operated for fracture femur surgeries in tertiary care hospital of North India. Patients were randomly divided into 3 groups ($n = 30$) Group A: received 0.5% hyperbaric bupivacaine 12.5 mg with 800 µg nalbuphine. Group B: Received 0.5% hyperbaric bupivacaine 12.5 mg with 25 µg butorphanol. Group C: Received 0.5% hyperbaric bupivacaine 12.5 mg with normal saline. Total volume injected was 3.0 ml. Duration of analgesia, mean VAS scores, requirement of rescue analgesia in 24 h along with intraoperative sensory or motor characteristics of block and hemodynamic parameters were studied. Statistical analysis was done using ANOVA with post-hoc Tukey test, Student's *t*-test and Chi-Square test.

Results: Demographic profile was comparable among all the three groups. Mean duration of postoperative analgesia was 348.33 ± 66.96 , 156.17 ± 43.9 and 110.36 ± 29.18 min in group A, B, and C, respectively ($P = 0.006$). Total doses of rescue analgesia were least in group A (32), followed by group B (42) and group C (64), respectively ($P = 0.001$). Group A had significantly earlier onset of sensory action ($P = 0.03$) as compared to group B and C. There was significant difference in sensory ($P = 0.08$) and motor duration ($P = 0.04$) among all the three groups. However, onset of motor block, haemodynamic profile and side effects were comparable among groups A, B, and C ($P > 0.05$).

Conclusion: Addition of 800 µg nalbuphine and 25 µg butorphanol as adjuvant to intrathecal bupivacaine has better outcome as compared to active placebo group. But intrathecal nalbuphine was more effective compared to intrathecal butorphanol in terms of prolonging postoperative analgesia, reducing rescue analgesic doses and onset of sensory block. However, hemodynamic profile and side effects were comparable among all groups.

Keywords: Butorphanol, nalbuphine, orthopaedic surgery anaesthesia, postoperative analgesia, spinal adjuvants, spinal anaesthesia

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Introduction

Postoperative pain during first 24 h can be distressful and also delays the movements of limb in patients undergoing lower limb orthopedic surgeries. Nalbuphine as well as butorphanol have been used as adjuvants in various doses, moreover all the studies mentioned their effectivity in prolonging postoperative analgesia compared to placebo.^[1,2] But there is no study comparing the efficacy of these two drugs as adjuvant to local anesthetics. We want to evaluate which of the two drugs is better for improving intraoperative as well as postoperative efficacy of intrathecal bupivacaine which is the most commonly used drug for spinal anesthesia. The primary outcome of study was to compare the duration of postoperative analgesia in patients undergoing orthopedic procedures of femur. The secondary outcome was measured as mean VAS scores, doses of rescue analgesia in 24 h, hemodynamics, block characteristics, and side effects.

Material and Methods

This prospective, randomized, double-blind study had been conducted on 90 adult patients of American Society of Anesthesiology (ASA) grade I/II, in the age group of 18–70 years of either sex undergoing lower limb surgeries for fracture femur. After approval from the institutional ethics committee a written informed consent in their vernacular language was sought. This study was registered with government of India trial registry (CTRI/2018/04/013214) and approved by the Institutional Ethics committee (Ref.no.: Patho 139/18 dated 12/02/2018).

Patients with pathological fractures or tumors, who refused to give consent; contraindications to spinal anesthesia such as coagulation abnormalities, local sepsis in spinal lumbar region, severe hypovolemia, increased intracranial pressure; history of allergy to study drugs; pre-existing diseases such as neurological, cardiovascular, metabolic, hepatic, respiratory, and renal were excluded from the study.

For randomization, computer generated random numbers were obtained and sealed in an envelope. The slip was taken out by senior anesthesiologist not involved in the study and the drugs were prepared according to the coded slip. In order to remove bias, both patient and assessor were blinded to group allotted. Group A ($n = 30$) received 0.5% hyperbaric bupivacaine 12.5 mg (2.5 ml) with 800 μ g nalbuphine (3.5 threads of insulin syringe and 1.5 threads of saline). Group B ($n = 30$) received 0.5% hyperbaric bupivacaine 12.5 mg (2.5 ml) with 25 μ g butorphanol (2.5 threads of insulin syringe plus 2.5 threads of saline). Group C ($n = 30$)

received 0.5% hyperbaric bupivacaine 12.5 mg (2.5 ml) with saline (5 threads of insulin syringe). Total volume injected had been kept constant, that is, 3 ml, so that blinding of drug was not affected.

All patients included in the study were subjected to detailed pre-anesthetic check-up and routine investigations. These patients were explained about visual analogue scale (VAS) that would be asked from them in postoperative period. VAS was measured as 10 cm line with 0 as no pain and 10 as maximum pain one can experience. VAS of 0–3 was categorized as mild, 4–7 moderate, and 8–10 severe pain.^[3]

These patients were restricted solid intake for 6 h and clear oral fluids for 2 h pre-operatively. Premedication was given in form of tablet alprazolam 0.5 mg one night prior and in the morning 2 h before surgery with sips of water. The vitals were checked in the preoperative room. After securing an intravenous cannula, an infusion of lactated Ringer's solution/normal saline 10 ml/kg was started in the operating room. Standard monitoring [pulse rate, oxygen saturation, non-invasive blood pressure (NIBP), and electrocardiography (ECG)] applied and was considered baseline.

Sub-arachnoid block was performed at the L3-4 interspace in sitting position using a 25 G quincke spinal needle. After confirming free flow of clear cerebrospinal fluid, the study drug was injected. After the intrathecal injection, the patient was made supine. All patients received oxygen at the rate 4 L/min via facemask irrespective of groups. In case spinal anesthesia failed due to technical difficulty or partial effect achieved, that is, sensory level less than T10 or motor level- less than Bromage scale of two; general anesthesia was given and that patient was excluded from statistical analysis.

The assessment of sensory block by pinprick was performed at every minute till maximum level achieved, which did not change with two readings taken 5 min apart. Time required for sensory block to reach level T10 dermatome level was considered as sensory onset. Sensory level was checked every 15 min until regression to two segments below the highest level and taken as duration of sensory block.

Motor effect was assessed using a modified Bromage scale^[4] each minute till maximum block, then every 30 min upto the return of normal motor functions. Motor onset was taken as time to reach Bromage 2 and time to regression as one grade lesser than maximum grade achieved considered duration of motor block.

Continuous intraoperative monitoring of vitals was done every 2 min for the first 10 min, at 5 min interval for the next 10 min and then at 10 min till the end of surgery.

These vitals were also noted in post-anesthetic care unit (PACU) for every 15 min for 2 h. In the ward every 4 h till 12 h and then at 24 h along with VAS. Duration of absolute analgesia defined as the time from intrathecal injection until VAS score ≤ 4 after which rescue analgesia was supplemented in the form of intramuscular diclofenac sodium 75 mg. Total analgesic requirements in the postoperative period was noted.

Patients were monitored for complications such as hypotension, bradycardia, nausea/vomiting, respiratory depression, pruritus, urinary retention. Hypotension ($< 20\%$ from baseline) was treated with an infusion of normal saline 10 ml/kg and with IV ephedrine 6 mg bolus. Bradycardia (< 60 bpm) was treated with atropine 0.6 mg IV bolus. Nausea/vomiting was treated with ondansetron 4 mg.

Sample determination and statistical analysis: Based on the results of pilot study conducted with 12 patients in each group, sample size of 26 patients per group was calculated to detect a difference of 28 min of duration of block between the two groups taking 0.05 alpha error and 80% power and a total sample size of 78. Considering 8–10% of failure rate sample size was increased to 90 with 30 patients in each group. [CONSORT flow diagram - Figure 1].

At the end of study the data compiled was decoded and statistically analyzed using – SPSS (Statistical Package for the Social Science) version 20.0.0 (SPSS Inc., Chicago, IL, USA). The continuous variables (quantitative data) were expressed as mean and standard deviation and statistically analyzed using ANOVA with Post-Hoc Tukey test. The categorical variables (qualitative data) were presented in frequency and percentage. Nominal data was analyzed with Chi-square test. The $P < 0.05$ value was considered statistically significant.

Results

Demographic profile (age, gender, BMI, ASA physical status, and duration of surgery) was statistically comparable among the three groups ($P > 0.05$) [Table 1].

When block characteristics were compared among the three groups, the sensory onset was significantly earlier and duration prolonged in group A $>$ group B $>$ group C ($P = 0.03$). The motor onset was similar but duration was prolonged in group A compared to group B and C ($P = 0.04$) [Table 2].

Intraoperative vitals such as heart rate, mean arterial pressure, respiratory rate, and SpO₂ were statistically comparable amongst all the three groups ($P > 0.05$).

The intergroup difference in mean total duration of analgesia as well as postoperative mean VAS scores at different time intervals is shown in Tables 2 and 3. The requirement of rescue analgesia in 24 h postoperatively was 32%, 42%, and 64% in group A, B, and C, respectively [Table 4].

Although minor side effects had been observed amongst the three groups but they were statistically comparable [Table 5]. None of the patient among three groups developed respiratory depression.

Discussion

Most of the times opioids have been used as adjuvants to intrathecal local anesthetics for either reducing the dose of local anesthetic agents or for prolonging the postoperative duration of analgesia. Opioids like morphine, fentanyl, sufentanil have been studied for this purpose but were associated with respiratory depression, nausea, vomiting, delayed voiding, and pruritus.^[5] Moreover, procurement of various opioids is becoming increasingly difficult due to increased restrictions imposed upon its dispensing and strict implementation of narcotic act because of addiction epidemic in our state. So, alternative drugs which lack major opioid side effects are being studied for the same purpose.

Nalbuphine as well as butorphanol have opioid agonist activity but chances of respiratory depression are less due to their action on kappa receptors. These drugs have ceiling effect on both analgesia as well as respiratory suppression.^[6,7] Although equipotent intravenous dose is 10 mg Morphine \sim 2 mg Butorphanol \sim 10 mg Nalbuphine, but no equipotent dose has been described in literature for its intrathecal use. The dose of 25 μ g of butorphanol as adjunct to local anesthetic have shown to produce best results with minimal side effects, whereas 800 μ g of nalbuphine has been described to be the most effective intrathecal dose. Culebras *et al.* used 0.2 mg compared to 0.8 mg intrathecally as adjuvant in cesarean patients. They concluded 0.2 mg was insufficient as compared to 0.8 mg nalbuphine for prolonging the duration of postoperative analgesia.^[1] Various other studies have also shown doses upto 800 μ g intrathecally to be effective when compared to placebo.^[8,9]

The butorphanol has been widely studied in the dose of 25 μ g for its intrathecal use and found to be safe and effective.^[2] There is no study comparing 25 μ g butorphanol with 800 μ g nalbuphine. So, this trial was carried out.

The primary aim of our study, that is, prolongation of duration of postoperative analgesia has been studied by various authors

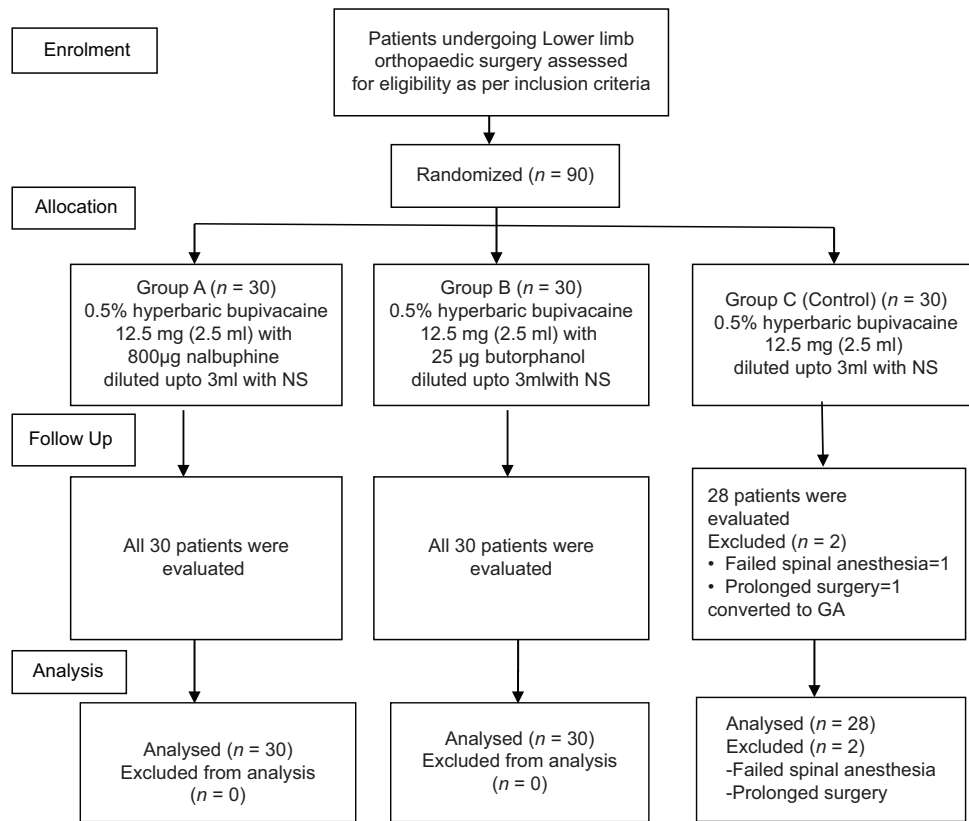


Figure 1: CONSORT – flow diagram

Table 1: Demographic Profile of Patients in Study Groups

	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=28)	P
Age (mean±SD)	49.67±15.81	49.2±13.76	45.61±16.23	0.548
BMI of Patients (Kg/m ²)	28.66±2.96	29.65±3.77	28.19±4.74	0.341
Gender				
Male (%)	46.66	60	64.28	0.325
Female (%)	53.33	40	35.71	0.364
ASA Grade				
I	17	12	15	0.400
II	13	18	15	0.412
Duration of Surgery				
Time (min)	117.33±7.4	113±12.36	115.71±6.34	0.185

Data are mean±SD for Age, BMI, duration of surgery, n=number of patients, P>0.05 insignificant

Table 2: Sensory, Motor Blockade and duration of analgesia in Study Groups

Parameters (minutes)	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=28)	P		
				A vs B	B vs C	A vs C
Onset of Sensory Block	2.9±0.71	3.3±0.7	3.68±0.48	0.03*	0.02*	0.00*
Duration of sensory block	144.83±6.09	141.83±2.78	138.75±5.38	0.01*	0.08*	0.00*
Onset of Motor Block	6.6±1.43	6.5±1.48	6.18±0.98	0.79	0.33	0.19
Duration of motor block	155.18±7.26	151±8.45	146±5.48	0.00*	0.04*	0.00*
Mean duration of analgesia	348.33±66.96	156.17±43.9	110.36±29.18	0.000*	0.05	0.00*

Data are mean±SD, n=number of patients, P<0.05=Significant*, P>0.05=Insignificant

who showed similar results to our study, that is, intrathecal nalbuphine 800 µg is effective for improving postoperative analgesia compared to other opioids or placebo.^[8-10]

Nalbuphine which acts primarily on kappa receptor and inhibits mu receptor, can reverse respiratory depression without reversing analgesia. Although being equipotent to

Table 3: A comparison of mean VAS in Study Groups

VAS (in minutes)	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)	A vs B (P)	A vs C (P)	B vs C (P)
0	0	0.07 ± 0.37	0.21 ± 0.83	0.321	0.164	0.38
60	0	0.67 ± 1.24	2.11 ± 0.92	0.005*	0.001*	0.001*
120	0.4 ± 0.77	2.33 ± 1.27	1.79 ± 1.87	0.001*	0.001*	0.195
240	1.43 ± 1.25	2.53 ± 1.68	1.07 ± 1.76	0.006*	0.005*	0.002*
480	2.8 ± 1.21	1.83 ± 2	0.79 ± 1.55	0.027*	0.001*	0.031*
720	1.9 ± 1.97	0.93 ± 1.72	0.93 ± 1.65	0.048*	0.048*	0.991
1440 (24 h)	0.4 ± 1.22	0	0.57 ± 1.43	0.078	0.624	0.062

*P ≤ 0.05 = Significant

Table 4: Number of Doses of Rescue Analgesia in 24 H in Study Groups

Rescue analgesia (N)	GROUP A (n=30) n (%)	GROUP B (n=30) n (%)	GROUP C (n=28) n (%)	P
1	28 (93.33)	20 (66.7)	3 (10.7)	0.000*
2	2 (6.67)	8 (26.7)	15 (53.6)	0.001*
3	-	2 (6.7)	9 (32.1)	0.006*
4	-	-	1 (3.6)	0.50
Total no. of doses	32	42	64	

Data are mean ± SD, n = number of patients; N = number of doses, P < 0.05 = Significant*, P > 0.05 = Insignificant

Table 5: Complications and adverse effects in various Study Groups

Complications	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=28)	Chi Square value	P
Nausea	2 (6.67)	5 (16.67)	3 (10.71)	1.50	0.47
Vomiting	0	1 (3.33)	1 (3.57)	0.38	0.82
Pruritus	1 (3.33)	0	0	1.29	0.52
Shivering	1 (3.33)	1 (3.33)	1 (3.57)	0.06	0.99
Hypotension	2 (7.14)	2 (6.67)	0	0.68	0.71
Bradycardia	1 (3.57)	0	0	1.29	0.52
Urinary Retention	0	0	0	-	-
Respiratory Depression	0	0	0	-	-
Dry Mouth	0	0	0	-	-

Data are number of patients with percentages (%)

morphine, it lacks the psychomimetic and other side effects. Due to its action on kappa I receptors, which mediates through spinal analgesia would potentiate the intrathecal effects of local anesthetics.^[6]

Mukerjee *et al.* found duration of analgesia to be 237.3 ± 5.64 min with 400 ug nalbuphine as compared to 278.5 ± 6.04 min with 800 ug nalbuphine ($P = 0.000$),^[11] whereas our results showed more duration of analgesia, that is, 348.33 ± 66.96 min as compared to above study may be because they had taken end point lesser than ours, that is, VAS ≥ 4 or due to regional/cultural differences.

In the present study, 25 µg butorphanol was significantly effective in increasing the duration of postoperative analgesia as compared to placebo which is inconcordance with other studies.^[2,3] Butorphanol is mixed agonist–antagonist opioid which also has maximum kappa affinity. Its affinity for various receptors have been described as kappa > delta > mu (25:4:1).^[7] However, Reddy *et al.* found duration of analgesia with 25 µg

butorphanol to be 282.8 ± 17.2 min, whereas our results showed 156.17 ± 43.9 min because we used lesser dose of hyperbaric 0.5% bupivacaine, that is, 12.5 mg versus 15 mg used by them.^[12]

But duration of postoperative analgesia with 25 µg butorphanol group was lesser than nalbuphine group probably because higher than equipotent dose of nalbuphine was used. Whereas hemodynamic parameters and block characteristics, that is, onset of sensory block, sensory duration and duration of motor block were statistically significant among all the three groups. Adding of these adjuvants to intrathecal bupivacaine have resulted in similar results with other studies.^[1,2,11]

Nalbuphine and butorphanol since they belong to same group of agonist–antagonist opioids, so they have similar side effects, that is, nausea/vomiting, hypotension, shivering, dizziness, vertigo, dry mouth, etc., In the present study we found nausea, vomiting, pruritus, shivering, hypotension, bradycardia to be present but statistically insignificant.

This is in concordance with various studies where these drugs were used intrathecally.^[8,9,11,2] The other side effects such as dizziness, vertigo, dry mouth had been reported with IV use were not seen in our patients.^[6]

Limitation of this study was that accuracy of the dose used in 0.5 fraction of insulin syringe cannot be assured. For postoperative analgesia, rescue and PRN analgesia used was same.

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Conflicts of interest

There are no conflicts of interest.

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