

Comparison of nalbuphine versus fentanyl as intrathecal adjuvant to bupivacaine for orthopedic surgeries: A randomized controlled double-blind trial

Ankit Sharma, Sujata Chaudhary, Mahendra Kumar, Ruchi Kapoor

Department of Anesthesiology and Critical Care, UCMS and GTB Hospital, Delhi, India

Abstract

Background and Aims: Intrathecal adjuvants are used with local anesthetics to prolong the duration and provide postoperative pain relief while minimizing the dose of local anesthetic. Nalbuphine is an agonist-antagonist opioid and provides prolonged duration of analgesia with fewer side effects of fentanyl such as pruritus, nausea, and vomiting. The aim of this study was to evaluate and compare the onset and duration of sensory and motor blockade, hemodynamic effects, duration of postoperative analgesia, and adverse effects of nalbuphine and fentanyl given intrathecally with hyperbaric 0.5% bupivacaine in orthopedic lower limb surgeries.

Material and Methods: Sixty six patients classified in American Society of Anesthesiology (ASA) classes I and II scheduled for orthopedic lower limb surgeries were enrolled. Patients were randomly allocated to receive 15 mg of hyperbaric bupivacaine with either 1 mg nalbuphine (group N), 25 µg fentanyl (group F) or 0.9% normal saline (group C) intrathecally.

Results: Patients who received intrathecal nalbuphine (group N) had a significantly delayed onset of sensory and motor block as compared to patients who received fentanyl (group F). The time to two segment regression was significantly prolonged in group F (122.05 ± 10.65 minutes) as compared to group N (114.55 ± 10.90 minutes) [$P < 0.05$]. The mean duration of motor blockade was significantly prolonged in group F (197.73 ± 15.09 minutes) as compared to group N (180.68 ± 15.68 minutes) [$P < 0.05$]. Duration of spinal analgesia was comparable in group N (323.18 ± 57.39 minutes) and group F (287.05 ± 78.87 minutes), both significantly more than group C (224.32 ± 42.54 minutes). Hemodynamic effects, 24-h rescue analgesic requirements, and incidence of side effects were comparable among group N and F.

Conclusion: Intrathecal nalbuphine in a dose of 1 mg is an equally useful alternative to fentanyl in a dose 25 µg when used as an intrathecal adjuvant to bupivacaine for lower limb surgeries. The prolonged duration of analgesia and no adverse effects makes it a good choice for the orthopedic procedures of lower limb.

Keywords: Fentanyl, intrathecal, Nalbuphine, Orthopedic surgery, spinal

Introduction

Orthopedic surgeries, primarily fractures of lower limb, present a unique challenge to anesthesiologists in terms of adequate analgesia along with fast motor recovery to ambulate the patient early. Neuraxial blockade is therefore the modality of choice as it provides adequate analgesia and

muscle relaxation intraoperatively along with prolonged postoperative analgesia while avoiding any postoperative delays in recovery. Neuraxial blockade provides a better safety profile by avoiding common side effects associated with drugs and invasive technique used in general anesthesia, besides the added advantages of rapid onset, effective pain

Address for correspondence: Dr. Ankit Sharma,
40/3, Ashok Nagar, P.O. Tilak Nagar, New Delhi - 110 018, India.
E-mail: ankitmamc@gmail.com

Access this article online

Quick Response Code:



Website:
www.joacp.org

DOI:
10.4103/joacp.JOACP_270_18

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How to cite this article: Sharma A, Chaudhary S, Kumar M, Kapoor R. Comparison of nalbuphine versus fentanyl as intrathecal adjuvant to bupivacaine for orthopedic surgeries: A randomized controlled double-blind trial. J Anesthesiol Clin Pharmacol 2021;37:529-36.

Submitted: 24-Oct-2018

Revised: 31-Aug-2019

Accepted: 06-Mar-2020

Published: 06-Jan-2022

relief, and cost-effectiveness. These advantages make this technique a better choice for lower abdominal, perineal and orthopedic lower limb surgeries.^[1,2] A single shot subarachnoid block is a quick and easy skill to learn and perform, comfortable for patient, involves relatively inexpensive equipment, and does not cause complications involved with epidural catheter, though combined spinal epidural anesthesia is considered as an equally good alternative technique.^[3,4]

Local anesthetic drugs such as bupivacaine and ropivacaine are commonly used via intrathecal route for lower limb surgeries to provide effective analgesia and sensory block for the surgery. Hyperbaric bupivacaine provides additional advantage of longer duration of effective blockade and pain relief with better control on the level of blockade achieved among conventional local anesthetics.^[5,6] Various adjuvants like opioids and alpha 2 agonists when added to local anesthetics prolong the duration of block and provide postoperative pain relief while minimizing the use of high dose of local anesthetic. Thus the patient remains free of pain for longer duration and can be ambulated early. Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. A number of opioids such as morphine, hydromorphone, fentanyl, sufentanil, and remifentanyl have been used via the intrathecal route.^[7]

Fentanyl is a commonly used intrathecal adjuvant and is used in a dose range of 10 µg to 50 µg. It has been proven to be an effective agent to prolong duration of sensory block and postoperative analgesia. Fentanyl is associated with side effects such as nausea, vomiting, pruritus, muscle rigidity, and respiratory depression. Nalbuphine belongs to mixed agonist-antagonist class of opioids (κ-agonist and µ-antagonist) with better features such as prolonged duration of analgesia while avoiding the side effects of fentanyl such as pruritus, nausea, and vomiting. Safety and advantages of Nalbuphine via intrathecal route have been ensured by multiple studies over the past three decades involving animals as well as human population. Neither Nalbuphine nor Fentanyl are FDA-approved for intrathecal usage, yet have been extensively used via the said route and safety of both the drugs has been well established.^[8-10]

On extensive search of literature (Pubmed and Medline), no study was found to have compared the efficacy and safety of 1 mg nalbuphine with 25 µg fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine. We conducted a prospective randomized controlled double blind study with an aim to compare the effects of nalbuphine versus fentanyl as intrathecal adjuvant to hyperbaric bupivacaine for lower limb orthopedic surgeries.

Primary:

The duration of spinal analgesia following intrathecal nalbuphine, fentanyl and saline as adjuvant to 0.5% hyperbaric bupivacaine in orthopaedic lower limb surgery.

Secondary:

- Time of onset, maximum level, time to achieve maximum level and duration of sensory block.
- Time of onset, intensity and duration of motor block.
- Postoperative pain assessment (VAS score) and total analgesic requirement in first 24 hours in three groups.

Material and Methods

The study was performed at a tertiary care hospital from October 2015 to April 2017 after obtaining approval from the Institutional Ethical Committee, patients undergoing elective orthopedic surgeries of lower limb were included in the study. Patients belonging to the American Society of Anesthesiology (ASA) grade I and II in the age group of 18 to 60 years and of height between 150 cm to 180 cm undergoing orthopedic lower limb surgery were included in the study. Patients with known allergy to the study drugs, patients with history of chronic pain or long term opioid use were excluded from the study. Written informed consent was obtained from all the participating patients.

A routine preanesthetic assessment was carried out and the procedure of spinal anesthesia was explained to the patients. During the preanesthetic check-up the patients were introduced to the concept of Visual Analogue Scale (VAS) for pain assessment. The patients were kept nil by mouth overnight and premedicated with oral tablet alprazolam 0.5 mg night before the surgery.

Using a computer generated random number table, patients were randomly allocated to three groups each comprising of 22 patients. Test solution was prepared by another anesthesiologist not involved in further assessment in study, as per randomized table number within sealed opaque envelopes, to ensure double blinding. Subarachnoid block was performed in all the patients, and 3.5 ml drug was injected via the intrathecal route:

- Group N: 15 mg 0.5% hyperbaric bupivacaine (3.0 ml) + 1 mg Nalbuphine (0.5 ml)
- Group F: 15 mg 0.5% hyperbaric bupivacaine (3.0 ml) + 25 µg Fentanyl (0.5 ml)
- Group C: 15 mg 0.5% hyperbaric bupivacaine (3.0 ml) + 0.5 ml normal saline.

Where needed, normal saline was used to dilute the study drug. Nalbuphine and fentanyl used in the study were preservative-free preparations.

Patients were shifted to the operating table and monitors were attached and the baseline values of the following parameters were noted:

1. Heart Rate
2. Blood Pressure (systolic, diastolic, and mean)
3. Peripheral oxygen saturation (SpO_2)
4. 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 L_3 - L_4 or L_4 - L_5 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' min. Immediately, the patient was placed in supine position and oxygen was administered at 5 L/min by face mask. Ringer's lactate solution was used for maintenance and replacement of blood loss (till allowable limit). The trial was retrospectively registered with CTRI. (CTRI/2018/01/011264).

Sensory parameters were observed and recorded intraoperatively and postoperatively. The time taken for the block to reach T_{10} 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).^[12] Onset of motor block was taken as Modified Bromage grade 3. Then reassessment was done every 30 min till complete recovery. Sedation scoring was done intraoperatively using 6-point Ramsay Sedation Score^[13] every 30 min intraoperatively and hourly for 2 h in the postoperative period. Heart rate, systolic, diastolic, and mean blood pressure values, and SpO_2 were recorded every 5 min for the first 15 min and then every 15 min for the rest of the operative period and every 1 h postoperatively till complete recovery.

Pain was evaluated postoperatively every 30 min for the first 2 h, and then at 4th, 8th, 12th h and after 24 h using a standard 10 cm linear Visual Analogue Scale (VAS).^[14] Duration of postoperative analgesia was taken as the time to requirement of first rescue analgesic ($\text{VAS} \geq 3$) from the time of intrathecal

injection. Injection diclofenac 75 mg intravenously was given as rescue analgesic and if $\text{VAS} \geq 3$ persisted after 30 min, injection paracetamol 1 g intravenously was also given. Patients were also observed for incidence of any adverse effects like nausea, vomiting, hypotension, bradycardia, and respiratory depression for up to 24 h postoperatively.

Statistical analysis

Calculation of sample size

Based on a previous study by Thote *et al.*, considering a variability of 11.3, 11.5, and 9.6 min in duration of sensory analgesia in patients receiving intrathecal fentanyl, nalbuphine, and patients in control group respectively, to estimate an absolute difference of 10 minutes in time for sensory regression of two levels and $\alpha = 5\%$ and power = 80%, a sample size of 22 cases were taken in each group.^[11]

Data obtained was analyzed using the software SPSS version 18. Quantitative variables such as age, height, weight, and duration of surgery were compared using the Student's t-test. Quantitative parameters measured repeatedly, such as heart rate and blood pressure readings were compared by repeated measure ANOVA and others such as mean VAS by one way ANOVA. A *P* value of less than 0.05 has been considered significant.

Results

A total of 73 patients planned for orthopedic lower limb surgery under subarachnoid block were enrolled and screened for eligibility for the study. Two patients did not meet the inclusion criteria and five patients did not give consent. Sixty six patients fulfilling the inclusion criteria were enrolled in the study. All the patients underwent orthopedic lower limb surgery under subarachnoid block. Data was analyzed for all 66 patients [Figure 1: CONSORT chart]. The three groups C, N, and F were comparable in terms of age, weight, and height of the patient, gender ratio, and duration of surgery [Table 1]. The mean time of onset of action in group C was 8.00 ± 1.38 min while it was 9.27 ± 1.45 min in group N and 7.73 ± 1.55 min in group F [Table 2]. The mean time of onset of action was significantly delayed in group N as compared to group C and F ($P < 0.05$). The maximum level of sensory block achieved in all three groups was T6. The minimum level of sensory block in group F and group C was T8, whereas in group N, in one patient, a block height of only T10 could be achieved [Figure 2]. The mean time to achieve maximum block height in group C was 13.45 ± 0.91 min while it was 14.00 ± 2.23 min in group N and 12.55 ± 1.26 min in group F [Table 2]. The mean time to reach maximum height of sensory block in Group N

Table 1: Demographic profile in three groups

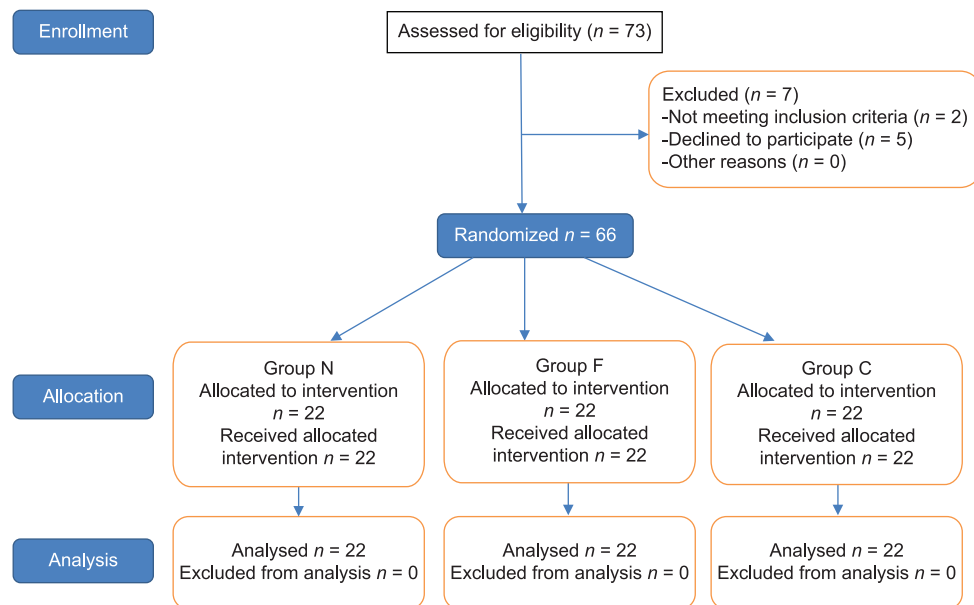
Parameter	Group C	Group N	Group F	P
Age (years)	29.27±10.94	34.95±14.88	29.32±11.43	0.232(NS)
Weight (kg)	63.05±5.59	63.64±5.45	65.36±6.11	0.383(NS)
Height (cm)	166.23±5.53	167.45±6.59	168.36±6.06	0.508(NS)
Sex Ratio	19/3 (M/F)	19/3 (M/F)	21/1 (M/F)	0.236(NS)
Duration (min)	98.86±11.95	108.41±15.99	104.32±14.98	0.096 (NS)

All statistics in mean±SD. $P<0.05$ significant. NS=Not Significant

Table 2: Sensory block characteristics

Parameter	Group C	Group N	Group F	P
Time to achieve T10	8.00±1.38	9.27±1.45	7.73±1.55	0.002*
Time to achieve maximum level	13.45±0.91	14.00±2.23	12.55±1.26	0.011†
Time to 2 segment regression	94.09±8.26	114.55±10.90	122.05±10.65	<0.001‡

All statistics in mean±SD minutes. $P<0.05$ significant. *Group N was significantly different from Group C & F †Group N was significantly different from Group F ‡All three groups were significantly different from each other

**Figure 1: CONSORT flow chart**

was significantly delayed as compared to group F ($P < 0.05$). The mean time to two segment regression in group C was 94.09 ± 8.26 min while it was 114.55 ± 10.90 min in group N and 122.05 ± 10.65 min in group F [Table 2]. The mean time to two segment regression was significantly prolonged in both group N and group F as compared to group C ($P < 0.05$). The time to two segment regression was significantly prolonged in group F as compared to group N ($P < 0.05$).

The onset of motor block (mean time to reach Bromage 3) in group C was 7.91 ± 1.44 min while it was 8.18 ± 2.46 and 6.73 ± 0.98 min in group N and F respectively. The mean time of onset was significantly faster in group F as compared to group N ($P < 0.05$). Mean time of onset of motor block in group C was comparable to the other two

groups [Table 3]. The duration of motor block (mean time to reach Bromage 0) in group C was 183.41 ± 14.59 min while it was 180.68 ± 15.68 min in group N as compared to 197.73 ± 15.09 min in group F [Table 3]. The mean duration of motor blockade was significantly prolonged in group F as compared to group C and group N ($P < 0.05$), with no significant difference between group C and N.

Duration of spinal analgesia was calculated as the time from subarachnoid block to the time to first rescue analgesic dose given at VAS score ≥ 3 for the first time. In group C the mean time to first rescue analgesic was 224.32 ± 42.54 min while it was 323.18 ± 57.39 and 287.05 ± 78.87 min in group N and F respectively. The time to the first rescue analgesic was significantly prolonged in group N and F as compared to group C. Duration of spinal analgesia was comparable among

group N and group F [Table 4]. The 24 hour rescue analgesic requirement was calculated on the basis of the number of rescue analgesic doses required in 24 h. The average number of rescue analgesic doses required in 24 h for group C was 2.36 ± 0.49 , for group N was 2.05 ± 0.49 and group F was 2.23 ± 0.43 . There was no statistically significant difference in the 24 hour rescue analgesia requirement among the three groups [Table 4].

Postoperative pain was assessed using Visual Analogue Scale (VAS). The mean VAS scores at different time intervals are shown in Figure 3. At 1.5 h postoperatively, the mean VAS score was significantly higher ($P < 0.05$) in group C (1.59 ± 1.76) as compared to group N (0.73 ± 1.45) and group F (0.73 ± 1.16). At 2 h postoperatively, the mean VAS score was significantly higher ($P < 0.05$) in group C (2.64 ± 1.96) as compared to group N (1.05 ± 0.89). The mean VAS scores at other time intervals were comparable among the three groups.

The patients were evaluated for hemodynamic changes intraoperatively every 5 min for first 15 min and then every 15 min till the end of surgery [Figures 4 and 5]. No incidence

of pruritus, respiratory depression, bradycardia, headache, or excessive sedation was observed in patients of either group. In group C, 3 out of 22 patients (13.63%) had hypotension. In group N and F, the incidence of hypotension was 2 (9.09%) and 6 (27.27%), out of 22 patients, respectively. In group C, 2 out of 22 patients (9.09%) complained of nausea. In group N and F, the incidence of nausea was 3 (13.63%) and 5 (22.72%), out of 22 patients, respectively. In group C, 1 out of 22 patients (4.54%) complained of vomiting. In group N and F, the incidence of vomiting was 0 and 3 (13.63%) out of 22 patients, respectively. The incidents of side effects were comparable among the three groups [Figure 6]. The mean sedation score across the three groups was 2.

Discussion

Single shot subarachnoid block is a commonly used technique of anesthesia for lower limb surgeries. Intrathecal adjuvants are used with local anesthetics to prolong the duration and provide postoperative pain relief while minimizing the dose of local anesthetic. Bupivacaine is one of the most commonly used drugs for subarachnoid block. However, use of bupivacaine alone for subarachnoid block provides limited duration of blockade (ranging from 60 to 120 min) and shorter postoperative analgesia. Opioids are commonly

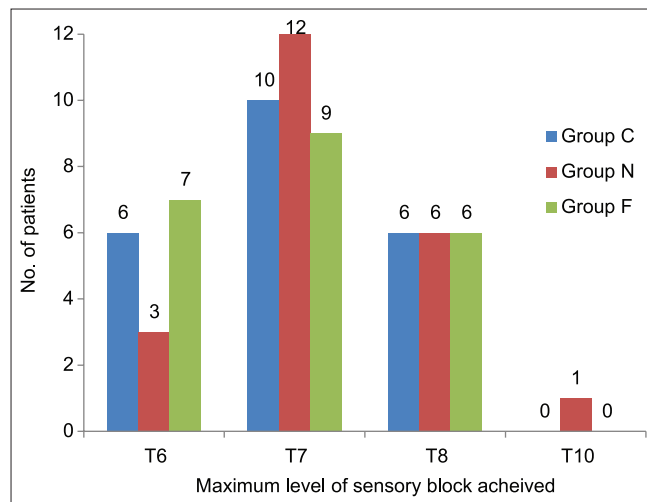


Figure 2: Distribution of highest level of sensory block

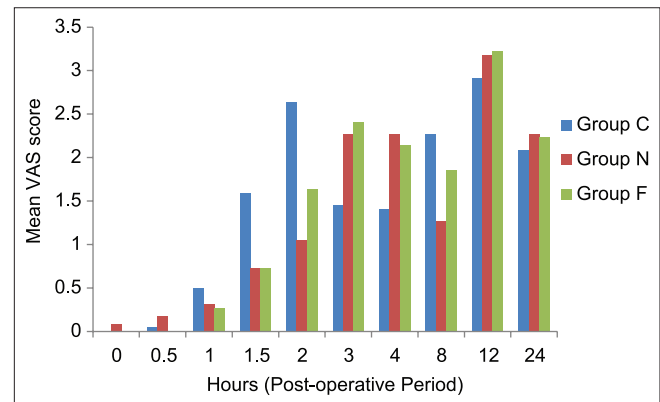


Figure 3: Mean VAS score in Post-operative period

Table 3: Motor block characteristics

Parameter	Group C	Group N	Group F	P
Onset of motor block (Time to Bromage 3)	7.91±1.44	8.18±2.46	6.73±0.98	0.017*
Duration of motor block (Time to Bromage 0)	183.41±14.59	180.68±15.68	197.73±15.09	<0.001†

All statistics in mean±SD minutes. $P < 0.05$ significant. *Group N was significantly different from Group F. †Group F was significantly different from Group N and C. No difference between group C and group N

Table 4: Duration of spinal analgesia and rescue analgesics required in 24 hours post-operatively

Parameter	Group C	Group N	Group F	P
Duration of spinal analgesia (minutes)	224.32±42.54	323.18±57.39	287.05±78.87	<0.000*
Total no. of rescue analgesic doses required	2.36±0.49	2.05±0.49	2.23±0.43	0.087(NS)

$P < 0.05$ significant. *Group C significantly different from Group N and Group F, no significant difference between Group N and F. NS=Not Significant

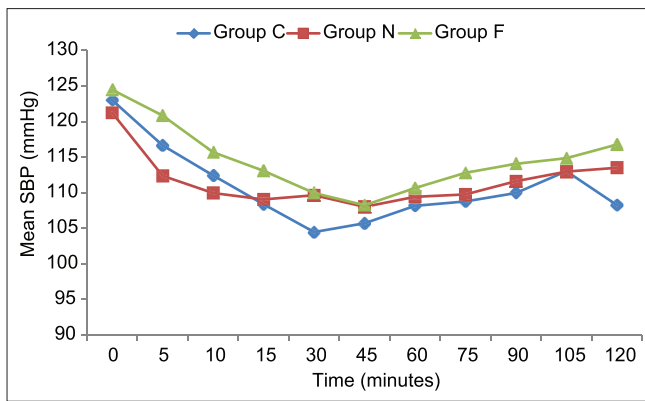


Figure 4: Intra-operative systolic blood pressure trends

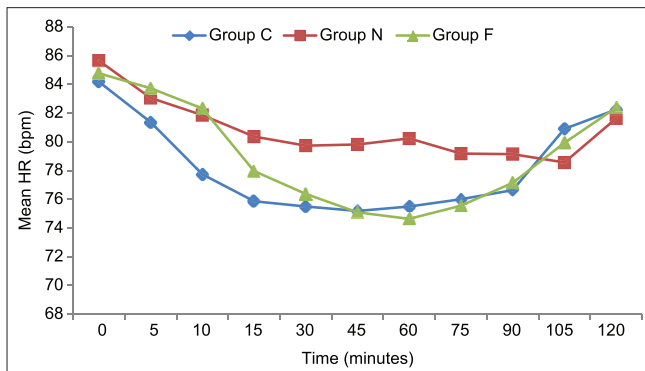


Figure 5: Intra-operative heart rate trends

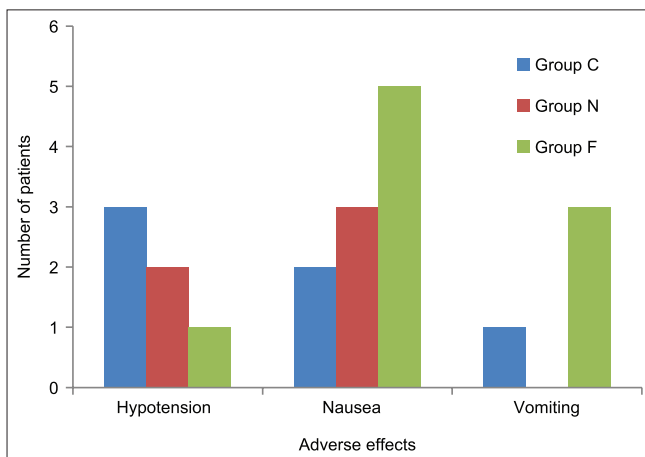


Figure 6: Incidence of adverse effects among the three groups

used as adjuvants to local anesthetics to prolong the duration of sensory and motor block with a better hemodynamic stability.

Nalbuphine is equianalgesic to morphine in terms of intramuscular and intravenous dosage, with similar onset and duration of analgesia. Nalbuphine depresses respiration as much as equianalgesic dose of morphine, but nalbuphine exhibits a ceiling effect to both analgesic effect and respiratory depression. The equipotent dose of nalbuphine to fentanyl is

2.5 mg and 25 µg. There is a lack of consensus on the dose of nalbuphine to be administered intrathecally for effective analgesia.^[15] The present study was aimed at comparing the duration of spinal analgesia using intrathecal nalbuphine versus fentanyl as adjuvant to 0.5% hyperbaric bupivacaine in orthopedic lower limb surgeries.

Moustafa MA *et al.* studied the intrathecal addition of 1 mg nalbuphine hydrochloride to a combination of 3 ml hyperbaric bupivacaine 0.5% and compared it with 0.2 mg morphine sulfate in patients undergoing total knee arthroplasty, and observed that patients receiving nalbuphine experienced lower incidence of vomiting and pruritus and there was no effect on the postoperative analgesic requirements or incidence of urinary retention, thus concluding that intrathecal addition of nalbuphine was safer when compared to morphine.^[16] Culebras X *et al.* used 0.2 mg, 0.8 mg, and 1.6 mg of nalbuphine as adjuvant to 10 mg of hyperbaric bupivacaine 0.5% and compared it with 0.2 mg morphine via intrathecal route in patients undergoing cesarean section and concluded that an intrathecal dose of 0.8 mg to 1.6 mg of nalbuphine was effective in providing good intraoperative analgesia.^[17]

Therefore we compared efficacy and side effect profile of intrathecal 1 mg nalbuphine versus 25 µg fentanyl as adjuvant in lower limb surgeries. In the present study, the addition of intrathecal nalbuphine (group N) significantly delayed the onset of sensory block (9.27 ± 1.45 min) as compared to patients receiving intrathecal fentanyl (7.73 ± 1.55 min) and control (8.00 ± 1.38 min). Our results are in contrast to the study by Shakoo S. *et al.* and Ahluwalia P. *et al.*, who reported earlier onset of sensory block in patients receiving intrathecal nalbuphine as compared to patients in control group.^[18,19] Manjula R. *et al.* compared 1 mg nalbuphine as an intrathecal adjuvant to control and Thote R. *et al.* compared fentanyl and nalbuphine and found no difference in onset of sensory block.^[11,20]

In the present study, the time taken for complete motor block (defined as the time to reach Bromage 3) was significantly earlier in patients receiving intrathecal fentanyl (6.73 ± 0.98 min) as compared to patients receiving intrathecal nalbuphine (8.18 ± 2.46 min), while both were comparable to control (7.91 ± 1.44 min). Gomaa H. *et al.* found intrathecal fentanyl to provide complete motor block significantly earlier than nalbuphine.^[23] The difference in the time of onset of sensory and motor blockade, even if significant, is not of much clinical importance. In the present study, duration of sensory block was defined as time to two segment regression and was found to be longer in patients receiving intrathecal fentanyl (122.05 ± 10.65 min) as compared to patients receiving nalbuphine (114.55 ± 10.90 min), which was in turn

significantly longer than control group (94.09 ± 8.26 min). Similar to our results, in the study by Mukherjee A. *et al.*, longer sensory block was observed in all the three groups receiving 0.2, 0.4, and 0.8 mg nalbuphine, as compared to control.^[21] The mean difference in the duration is of approximately 8 min, and may be of relatively low clinical significance perioperatively.

We found significantly prolongation of duration of motor blockade in patients receiving intrathecal fentanyl (197.73 ± 15.09 min) as compared to control (183.41 ± 14.59 min) and patients receiving intrathecal nalbuphine (180.68 ± 15.68 min), however, nalbuphine and control groups were comparable in this regard. Similar to our results, Mukherjee A. *et al.*, Manjula R. *et al.* and Gomaa H. *et al.* also reported duration of motor block to be comparable in patients with or without intrathecal nalbuphine.^[20,21,23] Short duration of motor block may be of clinical significance as early ambulation may be possible in postoperative period. In the present study, At 1.5 h postoperatively, the mean VAS in patients receiving nalbuphine (0.73 ± 1.45) and patients receiving fentanyl (0.73 ± 1.16) was lower than control (1.59 ± 1.76). At 2 h postoperatively, the mean VAS score in patients receiving nalbuphine (1.05 ± 0.89) was lower than control (2.64 ± 1.96). Lower VAS in postoperative period is of clinical importance in terms of providing longer and adequate analgesia to patients. In the present study, duration of spinal analgesia was defined as the time from subarachnoid block to the time to first rescue analgesic dose given at VAS score ≥ 3 for the first time. The time to the first rescue analgesia was significantly prolonged in patients receiving intrathecal nalbuphine (323.18 ± 57.39 min) and intrathecal fentanyl (287.05 ± 78.87 min) as compared to control, though duration of spinal analgesia was comparable in patients receiving nalbuphine and fentanyl intrathecally. Our results are in concurrence with results of previous authors who reported significant prolongation of duration of spinal analgesia with nalbuphine.^[11,21,22]

In the present study, the hemodynamics (blood pressure and heart rate) were found to be comparable among the three groups. In study by Sapate M. *et al.*, there was significant difference in hemodynamic profile, with higher mean heart rate, systolic, and diastolic blood pressure in patients receiving nalbuphine as compared to control group. In present study, the incidence of nausea, vomiting, and headache among all the three groups was comparable. The level of sedation in all the three groups was also comparable. Gomaa H. *et al.* and Jyothi B. *et al.* also reported no significant increase in the incidence of side effects with nalbuphine.^[23,24] Ahluwalia P. *et al.* reported incidence of nausea or vomiting in five patients ($n = 35$) receiving nalbuphine and two patients

in control ($n = 35$).^[19] In contrast to the above findings, Mukherjee A. *et al.* reported higher incidence of hypotension, nausea, vomiting, pruritus, and bradycardia in patients receiving 0.8 mg nalbuphine as compared to patients receiving 0.2 and 0.4 mg nalbuphine. Shakooch S. *et al.* and Thote R. *et al.* reported significantly increased incidence of sedation in patients receiving intrathecal nalbuphine. More studies may be required to confirm side-effect profile of intrathecal nalbuphine. In contrast to our results, Ahmed F. I. compared 25 mcg fentanyl with 0.8 mg nalbuphine as intrathecal adjuvant to 12.5 mg of 0.5% heavy bupivacaine for patients undergoing caesarean section and found fentanyl to be superior to nalbuphine in enhancing the onset of both sensory and motor block. Nalbuphine had a longer duration of postoperative analgesia with lesser incidence of pruritus and shivering.^[25] Prabhakaraiah U. N. et al compared 0.8 mg of nalbuphine with 25 μ g (0.5 ml) of fentanyl with 12.5 mg (2.5 ml) of 0.5% hyperbaric bupivacaine in lower abdominal surgeries and found onset, duration of sensory and motor block, and duration of effective analgesia to be comparable between both groups. Postoperative visual analog scale score was statistically highly significant ($P = 0.0007$) in nalbuphine group as compared to fentanyl group.^[26] The limitation of the present study would be a small sample size. Further studies are needed to be conducted in larger group of patients and those undergoing other surgical procedures, such as inguinal and lower abdominal surgeries.

The results of the present study indicate that the analgesia provided by nalbuphine is similar when compared to fentanyl when used as an adjuvant in subarachnoid block. We conclude that nalbuphine is an equally useful intrathecal adjuvant as compared to fentanyl in terms of duration of analgesia, postoperative analgesia requirements, and incidence of side-effects.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gonano C, Leitgeb U, Sitzwohl C, Ihra G, Weinstabl C, Kettner SC. Spinal versus general anesthesia for orthopedic surgery: Anesthesia drug and supply costs. *Anesth Analg* 2006;102:524-9.
2. Schuster M, Gottschalk A, Berger J, Standl T. A retrospective comparison of costs for regional and general anesthesia techniques. *Anesth Analg* 2005;100:786-94.
3. Brull R, MacFarlane AJR, Chan VWS. Spinal, epidural, and caudal anesthesia. In: Miller RD, editor. *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015. p. 1684-716.

4. Sherwood ER, Williams CG, Prough DS. Anesthesiology principles, pain management, and conscious sedation. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston Textbook of Surgery. 19th ed. Philadelphia, PA: Elsevier Saunders; 2012. p. 389-417.
5. Atef H, El-Kasaby A, Omera M, Badr M. Optimal dose of hyperbaric bupivacaine 0.5% for unilateral spinal anesthesia during diagnostic knee arthroscopy. *Local Reg Anesth* 2010;3:85-91.
6. Rani CR, Rama Krishna NSV, Babu VH, Rao ASK. A comparative study of intrathecal hyperbaric bupivacaine 0.5% & intrathecal isobaric ropivacaine 0.5% for quality and duration of anesthesia and post-operative analgesia in patients undergoing lower limb surgeries. *J Evol Med Dent Sci* 2014;3:2886-91.
7. Ben David B, Solomon E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small dose dilute bupivacaine: Better anaesthesia without prolonging recovery. *Anesth Analg* 1997;85:560-5.
8. Rawal N, Nuutinen L, Raj PP, Lovering SL, Gobuty AH, Hargardine J, *et al.* Behavioral and histopathologic effects following intrathecal administration of butorphanol, sufentanil, and nalbuphine in sheep. *Anesthesiology* 1991;75:1025-34.
9. Lin ML. The analgesic effect of subarachnoid administration of tetracaine combined with low dose morphine or nalbuphine for spinal anesthesia. *Ma Zui Xue Za Zhi* 1992;30:101-5.
10. Gupta K, Rastogi B, Gupta PK, Singh I, Bansal M, Tyagi V. Intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs under subarachnoid block: A comparative evaluation. *Indian J Pain* 2016;30:90.
11. Thote RJ, Lomate P, Gaikwad S, Paranjpe JS, Mane M. Comparison among intrathecal fentanyl and nalbuphine in combination with bupivacaine and plain bupivacaine for lower limb surgeries. *Int J Recent Trends Sci Tech* 2015;14:361-6.
12. Hocking G, Wildsmith JAW. Intrathecal drug spread. *Br J Anaesth* 2004;93:568-78.
13. Ramsay MA, Savage TM, Simpson BR. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974;22:656-9.
14. Huskisson EC. Visual analogue scale. In: Melzack R, editor. *Pain Measurement and Assessment*. New York: Raven Press; 1983. p. 33-7.
15. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In: Brunton L, Chabner B, Knollman B, editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. USA: Goodman & Gilman's; 2011. p. 483-90.
16. Moustafa MA, Saleh RS. Nalbuphine added to intrathecal morphine in total knee arthroplasty; effect on postoperative analgesic requirements and morphine related side effects. *Alexandria J Med* 2012;48:175-8.
17. Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecalnalbuphine, compared with intrathecal morphine, after cesarean delivery: An evaluation of postoperative analgesia and adverse effects. *Anesth Analg* 2000;91:601-5.
18. Shakoo S, Bhosle P. Intrathecalnalbuphine: An effective adjuvant for post-operative analgesia. *Innovative J Med Health Sci* 2004;4:79-82.
19. Ahluwalia P, Ahluwalia A, Varshney R, Thakur S, Bhandari S. A prospective randomized double blind study to evaluate the effects of intrathecalnalbuphine in patients of lower abdominal surgeries under spinal anaesthesia. *Int J Sci Stud* 2015;3:19-23.
20. Manjula R, Chaithra GV, Gandhi A, Ranjan US, Prabhu AV. Comparative study of bupivacaine with nalbuphine and bupivacaine alone for post-operative analgesia in subarachnoid block for lower limb surgeries-prospective randomised study. *J AnestInten Care Med* 2017;2:1-5.
21. Mukherjee A, Pal A, Agrawal J, Mehrotra A, Dawar N. Intrathecalnalbuphine as an adjuvant to subarachnoid block: What is the most effective dose? *Anesth Essays Res* 2011;5:171-5.
22. Sapate M, Sahu P, Thatte WS, Dubey R. A randomized, double blind, control study of the effects of adding nalbuphine to spinal bupivacaine for lower abdominal surgeries in elderly patients. *Anaesth Pain Intensive Care* 2013;17:145-8.
23. Gomaa HM, Mohameda NN, Zoheira HAH, Alib MS. A comparison between post-operative analgesia after intrathecalnalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section. *Egyptian J Anaesth* 2014;30:405-10.
24. Jyothi B, Gowda S, Shaikh SI. A comparison of analgesic effect of different doses of intrathecalnalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal and orthopedic surgeries. *Indian J Pain* 2014;28:18-23.
25. Ahmed FI. Intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: A randomized double-blind study. *Research and Opinion in Anesthesia and Intensive Care* 2019;6:112.
26. Prabhakaraiah UN, Narayanappa AB, Gurulingaswamy S, Kempegowda K, Vijaynagar KA, Hanumantharayappa NB, Ramegowda DS. "Comparison of nalbuphine hydrochloride and fentanyl as an adjuvant to bupivacaine for spinal anesthesia in lower abdominal surgeries:" A randomized, double-blind study. *Anesthesia, essays and researches* 2017;11:859.