Original Article

A double-blind prospective randomised controlled clinical study comparing 0.5% hyperbaric bupivacaine with nalbuphine and 0.5% hyperbaric bupivacaine for spinal anaesthesia in lower limb orthopaedic surgeries

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Abstract

Background: Intrathecal nalbuphine is one such opioid, highly lipid soluble with an agonist action at the kappa and antagonist activity at the muopioid receptors, known cardiovascular stability, minimal dose and volume of this drug that can be added to a local anaesthetic agent.

Methods: This prospective randomised double-blind study was conducted to evaluate the effects of adding nalbuphine to 0.5% hyperbaric bupivacaine in spinal anaesthesia to know the efficacy, duration of analgesia, incidence of side effects and complications. Sixty American Society of Anesthesiologists (ASA) grade I and II patients were randomly allocated to Group A and Group B of 30 each who received 0.4 mL (0.4 mg) of nalbuphine and 0.4 mL of normal saline added to 3 mL (15 mg) of 0.5% hyperbaric bupivacaine, respectively. Intraoperative haemodynamic parameters, onset, duration of sensory and motor block, visual analogue scale (VAS) score, duration of effective analgesia and possible side effects were monitored and compared.

Results: There was no statistically significant difference in the haemodynamic parameters, onset of blockade, duration of motor blockade and side effects. However, in two-segment regression, time of sensory blockade, duration of effective analgesia and VAS scores in Group A were found statistically significantly higher ($P < 0.001$) compared to Group B.

Conclusions: Intrathecal nalbuphine used as adjuvant to bupivacaine prolongs duration of effective analgesia, without any significant side effects with stable haemodynamic parameters.

Keywords: Bupivacaine, duration of analgesia, nalbuphine, lower limb orthopaedic surgeries, spinal anaesthesia

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INTRODUCTION

Spinal anaesthesia is the most popular regional anaesthesia technique. Spinal anaesthesia is advantageous in that it uses small dose of anaesthetic, is simple to perform and offers rapid onset of action, reliable surgical analgesia and good

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muscle relaxation. These advantages are sometimes offset by a relative short duration of action and appearance of pain when it wears off.

The discovery of opioid receptors in the spinal cord has opened new avenues for relief of pain, both in intra- and post-operative periods by administering them through intrathecal as well as through epidural route. The addition of opioids also has the advantage of synergistic action along with local anaesthetic agents, decreased dose of local anaesthetic agents and prolonging the pain relief up to several hours into the post-operative period. Intrathecal nalbuphine is one such opioid, with known cardiovascular stability, minimal dosage requirement. Further, minimal volume of this drug that can be added to a local anaesthetic agent like bupivacaine makes it an ideal opioid drug for study. Nalbuphine is a highly lipid-soluble opioid with an agonist action at the kappa and antagonist activity at the mu[1,2] opioid receptors. Nalbuphine being an agonist-antagonist is less likely to cause side effects because of its action at kappa receptors.

Hence, this study was aimed to evaluate the effects of adding nalbuphine to 0.5% hyperbaric bupivacaine in spinal anaesthesia to know the efficacy, duration of analgesia, incidence of side effects and complications.

MATERIAL AND METHODS

After obtaining ethical clearance from our Institutional Ethics and Scientific Committee, the study was conducted. study in 60 adult patients posted for elective lower limb orthopaedic surgeries at our institute from March 2014 to February 2015.

Patients belonging to American Society of Anesthesiologists (ASA) physical status classification I and II, aged 18-60 years, weighing 40-70 kg, with a height 145-160 cm who consented and valid informed consent were included, while patients with severe respiratory, cardiovascular, renal and endocrine disorders, allergic to the local anaesthetics and opioids, receiving phenothiazine, other tranquilisers, hypnotics or other central nervous system depressants, with coagulation disorders and local sepsis, pregnant and lactating women, inadequate subarachnoid blockade and who are later supplemented by general anaesthesia were excluded from our study.

Sample size was calculated by considering two-sided significance level of 95% and power of study as 80%, and using the results of the previous studies,[3,4] the sample size was calculated as 30 in each group. Patients were allocated in a randomised manner by computer-generated randomisation chart. Sixty patients were randomly divided into Group A and Group B of 30 each. The participants were received 0.4 mg of nalbuphine made up to 0.4 mL of volume with normal saline (Group A – study group) and 0.4 mL of normal saline (Group B – control group), respectively, added to 3 mL (15 mg) of 0.5% hyperbaric bupivacaine (total volume 3.4 mL).

Pre-anaesthetic check-up was done 1 day before the surgery. The procedure of spinal anaesthesia was explained and educated about the use of visual analogue scale (VAS); written informed consent was obtained. Patients were asked to be kept nil per orally for at least 6 H before surgery. Equipment and drugs for resuscitation, airway management and ventilation were kept ready, in anticipation of any untoward events. The study drug was prepared according to the randomisation list by the anaesthesiologist and administered intrathecally to the patient but did not further participate in the observation or collection of data. Both the patient and the observer were unaware to the patient's group assignment, and all observations were recorded by the observer blinded to the randomisation schedule. After shifting the patient to the operation theatre, intravenous (iv) access was secured with 18-gauge cannula and was pre-loaded with 10 mL/Kg of Ringer lactate. The monitors were connected to the patient and basic vitals such as heart rate, non-invasive blood pressure, peripheral oxygen saturation) and respiratory rate were recorded before spinal anaesthesia. Sedatives and hypnotics were avoided in pre-, intra- and post-operative period. Under all aseptic conditions, spinal anaesthesia was performed with the patient in the lateral decubitus position using a 25-gauge Quincke needle at the L3–L4 or L4–L5 interspaces; following free flow of cerebrospinal fluid, respective drug was injected into subarachnoid space. Patients were positioned in supine immediately after injection. Intra-operatively, the following vital parameters were monitored and recorded for every 5 min for first 30 min, interval of 10 min up to 60 min, interval of 30 min up to 120 min, and interval of 60 min up to 300 min from the time of injection. Level of sensory block was assessed by pinprick method and motor block by modified Bromage scale,[5] at 1, 2, 3, 4, 5 and 10 min, then every 30 min up to 300 min after subarachnoid block (SAB).

Sensory blockade was assessed by pinprick method. The time of onset was assessed from time of injection of the drug into the subarachnoid space to loss of pinprick sensation at T10 dermatome.[5] The time to achieve maximum sensory block was assessed from time of injection of drug to loss of pinprick sensation at the highest dermatomal level. The duration of sensory block was assessed by two-segment regression time from highest level of sensory blockade.[5]

Motor blockade was assessed by modified Bromage scale.[6] The time interval between injection of drug into subarachnoid space to the patient's inability to lift the straight extended leg was taken as onset time. The time to achieve maximum motor blockade was assessed from time of injection of the drug to maximum degree of motor block. The duration of motor block was assessed from the time of onset to modified Bromage scale grade 1.[5]

Postoperatively, the pain score was recorded by using VAS[7] between 0 and 10 (0 = no pain, 10 = worst pain). The duration of effective analgesia was calculated from the intrathecal injection of drug to first analgesic request by the patient or VAS was 3.5 or more. VAS was assessed every 30 min up to 300 min after SAB or until VAS ≥ 3.5.[5] When VAS ≥ 3.5 or first analgesic request by patient, rescue analgesic in the form of injection diclofenac 75 mg im was given and the study ended. The following side effects such as nausea, vomiting, pruritus, hypoxaemia, respiratory depression, sedation, hypotension and bradycardia were recorded and treated in both intra- and post-operative period according to the institutional protocol.

Statistical analysis

Student's *t*-test and Chi-square Test were used for inferential statistical analysis. Student *t*-test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (intergroup analysis) on metric parameters. Chi-square/Fisher's exact test was used to find the significance of study parameters on categorical scale between two or more groups. A $P < 0.05$ was considered statistically significant. The statistical software namely Statistical Package for the Social Sciences (SPSS) version 15.0 was used for the analysis of the data.

RESULTS

This double-blind prospective randomised controlled clinical study included 60 adult patients who were

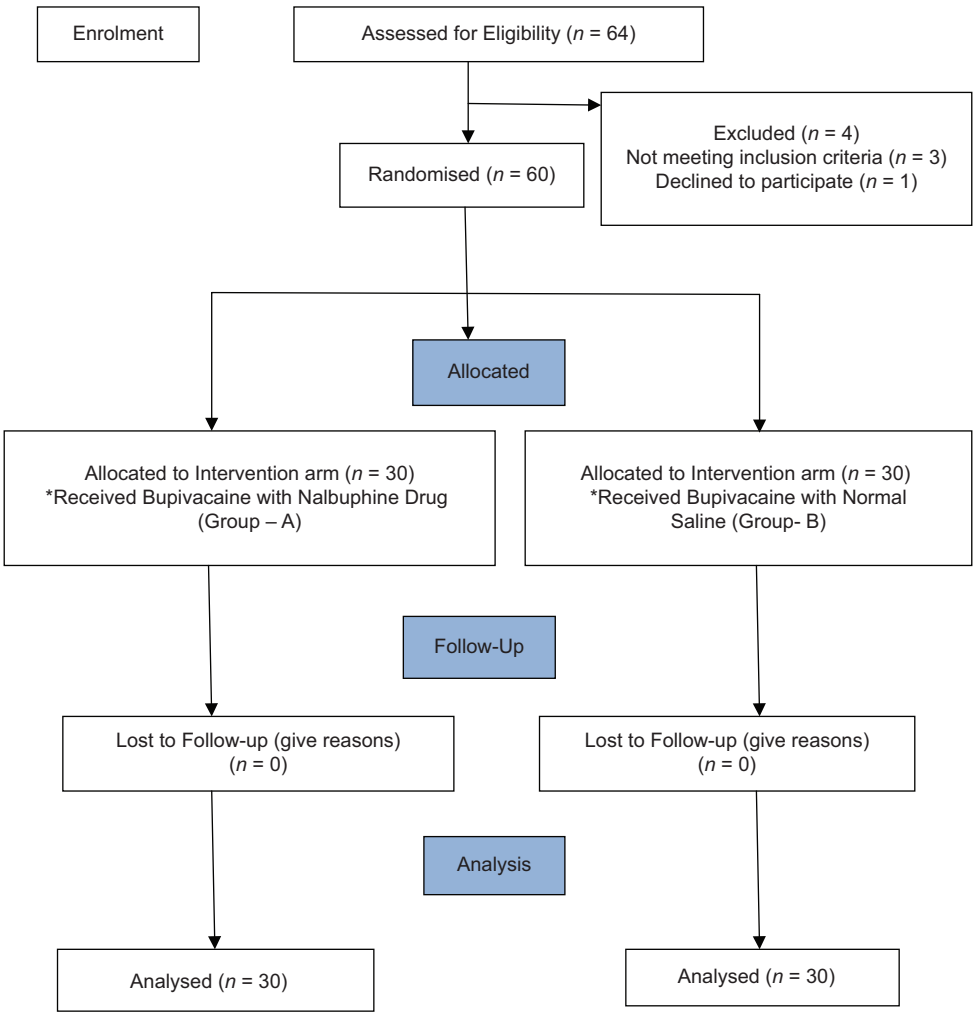

Figure 1: Study plan

randomly divided into Group A and Group B (Figure 1). The two groups of patients included in the study did not differ significantly with respect to age, sex, body weight, height type of surgery and haemodynamic parameters (Table 1). Comparison of sensory, motor block and duration of analgesia is shown in Table 2. Group A patients had a higher statistically significant two segment regression time of sensory block (147.0 ± 18.8 Vs 94.0 ± 16.5 min) ($p < 0.001$); and duration of effective analgesia (264.4 ± 11.7 Vs 168.8 ± 10.0, $P < 0.001$) compared to Group B. (Table 2).

Table 1: Comparison of demographic data and duration of surgery*

Variable	Group A (n=30)	Group-B (n=30)	*P-value*
Age (years)	38.3±8.1	39.6±8.4	0.545
Sex (Male: Female)	15:15	16:14	1.000
Height (cm)	155.6±3.1	155.1±2.9	0.520
Weight (kg)	62.1±5.9	62.7±5.8	0.674
Duration of surgery (min)	122.5±4.3	122.6±4.0	0.901

*Data are presented as mean±standard deviation

Table 2: Comparison of sensory, motor block and duration of analgesia*

Characteristics	Group A (n=30)	Group B (n=30)	*P-value*
Onset of sensory block (s)	98.0±36.9	96.0±37.3	0.955
Two segment regression time of sensory block (min)	147.0±18.8	94.0±16.5	<0.001
Onset of motor block (s)	160.0±36.4	162.0±35.8	0.926
Duration of motor block (min)	146.0±18.9	146.0±18.9	>0.99
Duration of effective analgesia (min)	264.4±11.7	168.8±10.0	<0.001

*Data are presented as mean±standard deviation

Comparison of side effects is shown in Table 3. Common side-effects included hypotension, bradycardia, nausea/vomiting. There was no statistically significant difference in the occurrence of side-effects between the two groups. None of the patients had developed pruritus, respiratory depression or urinary retention.

Table 3: Comparison of side effects

Characteristics	Group A (*n*=30) No. (%)	Group B (*n*=30) No. (%)	*P-value*
Hypotension	0	1 (3.3)	>0.99
Bradycardia	1 (3.3)	0	>0.99
Nausea/vomiting	2 (6.7)	0	>0.99

Comparison of duration of effective analgesia is shown in Figure 2. Duration of effective analgesia and VAS scores in Group A were found statistically significantly higher ($P < 0.001$) compared to Group B.

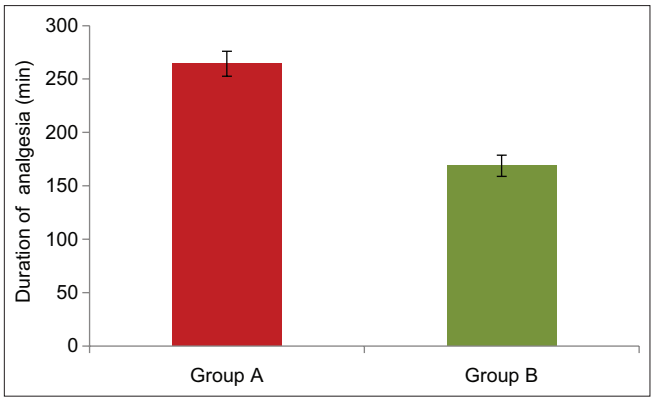

Figure 2: Comparison of duration of effective analgesia

DISCUSSION

SAB is a commonly employed anaesthetic technique for lower abdominal and lower limb surgeries. In recent years, the use of intrathecal opioids has the advantage of synergistic action along with local anaesthetic agents, decreased dose of local anaesthetic agents and prolonging the pain relief up to several hours into the post-operative period. In the present study, intrathecal nalbuphine is an opioid, structurally related to oxymorphone, highly lipid-soluble opioid with an agonist action at the kappa and antagonist activity at the mu[1,2] opioid receptors. Nalbuphine being an agonist antagonist is less likely to cause side effects such as pruritus, nausea, vomiting, urinary retention, excessive sedation and respiratory depression.

Earlier studies[3,8,9] found that 0.4 mg of nalbuphine has prolonged duration of analgesia and significantly lesser side effects compared to other dosages. Hence, we choose 0.4 mg of nalbuphine as an additive. The patients studied were found statistically insignificant with respect to age, sex, height, weight and duration of surgery. The type of surgeries performed was almost identical in both the groups to avoid variations in the intra- and post-operative outcome of the patients.

In the present study, there was no statistically significant difference in the haemodynamic parameters in Group A and Group B, the study results are in accordance with earlier reports.[5,10-12] In a study[12] conducted in 60 female patients belonging to ASA grade I/II scheduled for abdominal hysterectomy, to evaluate the effects of addition of 1 mg of nalbuphine intrathecally, even higher doses of nalbuphine (1 mg) did not show any significant difference probably due to sympathetic sparing effect of nalbuphine.[8]

However, the present study results are contradictory to observations reported in some studies[13,14] where a statistically significant difference was noted, but it was clinically insignificant and did not require any intervention.

The onset of sensory blockade in Group A was 98.00 ± 36.89 Sec compared to 96.00 ± 37.28 Sec in Group B, which was not statistically significant ($P = 0.955$). The present study results are in accordance with previous studies.[5,12-14] In a double-blind randomized study[3] on 100 adult patients admitted for lower abdominal and orthopaedic procedures, found that onset of sensory blockade with different doses nalbuphine (0.8 mg, 1.6 mg, 2.4 mg) as compared to control group was not significant statistically ($P = 0.62$). It signifies that an incremental dose of nalbuphine does not alter the onset of sensory block. The duration of sensory block was assessed by two-segment regression time from highest level of sensory blockade. It was prolonged in Group A (147.00 ± 18.78 min) compared to Group B (94.00 ± 16.52 min) which was statistically very significant ($P < 0.001$) probably due to agonist action of nalbuphine on kappa receptors.[12] The present study results are in accordance with other studies.[5,9,12,14,15]

The onset of motor blockade in Group A was 160.00 ± 36.38 sec compared to Group B was 162.00 ± 35.75 sec, which was not statistically significant ($P = 0.926$), and the results are also in accordance with previous studies.[5,12,14,16] This can be explained on the basis of motor sparing effect of nalbuphine.[8] The duration of motor blockade in Group A was 146.00 ± 18.86 min compared to 146.00 ± 18.86 min in Group B, which was not statistically significant ($P = 1.000$). The present study results are in accordance with other reports.[10,12] Similar studies[5,9] done with different doses of nalbuphine ([0.2 mg, 0.4 mg] and [0.2 mg, 0.4 mg, 0.8 mg]) found that results are comparable with control group ($P > 0.05$). From the above studies, it can be inferred that even with usage of different doses, there is no change in duration of motor blockade which can be attributed to the motor nerve-sparing effect of nalbuphine.[8]

In the present study, VAS score at 90 min, 120 min and 150 min was found less in Group A compared to Group B, which was statistically significant ($P < 0.001$). Similar results were reported in other studies[3,9,11] where lesser VAS score was reported in nalbuphine group compared with control group. The duration of effective analgesia was assessed from the intrathecal injection of drug to first analgesic request by the patient or VAS score of 3.5 or more. It was prolonged in Group A (264.37 ± 11.71 min) compared to Group B (168.83 ± 9.97 min), which was statistically very significant ($P < 0.001$). The present study results are similar to that reported in another study[8] where prolonged duration of analgesia was observed in nalbuphine group (464 ± 20.02 min) as compared to 158.5 ± 19.03 min in the control group ($P < 0.001$). Similar results are reported in previous studies.[9,14,16] In a study[5] significantly prolonged duration of analgesia with different doses of nalbuphine (0.2 mg, 0.4 mg, 0.8 mg) compared to control group ($P < 0.001$) was reported. Increasing nalbuphine dosage from 0.8-1.6 mg and 2.4 mg did not increase analgesic efficacy as nalbuphine attains analgesic ceiling effect at 0.8 mg dosage in another study.[3]

In the present study, nausea/vomiting was noted in 2 (6.7%) patients of Group A whereas none experienced in Group B. Bradycardia was recorded in one (3.3%) patient of Group A compared to none in Group B. Hypotension was recorded in one (3.3%) patient of Group B compared to none in Group A. A study[5] reported hypotension in 8 patients with 0.8 mg nalbuphine dose and 2 patients with 0.4 mg dose compared to none in present study Group A. Significant side effects were observed with 0.8 mg probably due to higher dose of nalbuphine. None of the patients in our study had μ receptor-related side effects such as urinary retention, pruritus and respiratory depression because nalbuphine is a μ receptor antagonist.

The study was limited only to ASA I and II grade. From the present study, we concluded that addition of nalbuphine hydrochloride (0.4 mg) intrathecally to 0.5% hyperbaric bupivacaine in the lower limb orthopaedic surgeries prolongs duration of sensory blockade, duration of effective analgesia with minimal side effects and more stable haemodynamic parameters in the perioperative period.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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