Original Article

Effects of Intrathecal Nalbuphine as an Adjuvant for Postoperative Analgesia: A Randomized, Double Blind, Control Study

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Abstract

Context: Opioids as adjuvants have been frequently used to prolong the neuraxial blockade for postoperative analgesia and are known to cause adverse effects. Nalbuphine, as an opioid with minimal adverse effects was tried for its effectiveness. **Aims:** Research was done to evaluate the effects of intrathecal Nalbuphine on the speed of onset of sensory and motor blockade, duration of analgesia and its side effects. **Materials and Methods:** Randomized clinical trial with a sample size of 60 adults in two groups of 30 each scheduled for lower abdominal and orthopaedic surgeries were included. Group 1 received 3 ml of hyperbaric bupivacaine 0.5% + 0.8 ml nalbuphine (0.8 mg) intrathecally, whereas group 2 received 3 ml of hyperbaric bupivacaine 0.5% + 0.8 ml of normal saline intrathecally. The onset of sensory and motor blockade, regression time of sensory blockade, duration of motor blockade, and analgesia, visual analogue scale (VAS) pain score and side effects were compared between the groups. **Statistical Analysis Used:** All the data was analyzed statistically and the significance was measured as probability of occurrence by the Student's *t*-test and Mann–Whitney U test. The values were expressed as mean ± the standard deviation and a *P* value less than 0.05 was considered statistically significant. **Results:** The onset of sensory blockade was slower with increased duration of analgesia. Regression time of sensory blockade and duration of effective analgesia was prolonged in the study group with no significant side effects. **Conclusions:** Improvement in the duration of sensory and motor blockade with minimal side effects was observed, thus proving that it is an effective intrathecal adjuvant for postoperative analgesia.

Keywords: Intrathecal administration, nalbuphine, sensory and motor blockade

Introduction

Spinal anesthesia was introduced about a 100 years back and still remains the most popular regional anesthetic technique. However, the local anesthetic drugs do not have the advantage of prolonged postoperative analgesia. Routinely, 0.5% hyperbaric bupivacaine is used as a local anesthetic drug for lower abdominal and orthopedic surgeries. Analgesia is one of the prime demands of patients post operatively. Various modes of pain relief have been used to overcome pain but opioids provide the most effective pain relief and are a standard of care.[1]

Nalbuphine is a semi-synthetic opioid with mixed mu antagonist and kappa agonist properties. Previous studies have shown that intrathecal administration of nalbuphine produces significant analgesia with minimal pruritus and respiratory depression.[2] Thus, we thought that it may be a good alternative to other opioid drugs.

Previous studies have compared intrathecal doses of nalbuphine of 0.2, 0.4, 0.8, and 1.6 mg and found that 0.8 mg is an effective dose.[3,4]

We therefore intended to study the effect of 0.8 mg nalbuphine added as an adjuvant to bupivacaine and compared it with plain bupivacaine to establish the advantage in terms of duration and quality of postoperative analgesia and side effects, if any.

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Materials and Methods

The study was approved by the institutional ethics committee and written informed consent was obtained from all patients before participation. Sixty patients, ASA physical status I and II, aged 18–50 years, scheduled for elective lower abdominal and orthopedic surgeries, of duration less than 3 h, under sub arachnoid block (SAB), were included in the study. Patients were randomly allocated to one of the two groups (n = 30). Group 1 received 3 ml of hyperbaric bupivacaine 0.5% + 0.8 ml nalbuphine (0.8 mg) intrathecally, whereas group 2 received 3 ml of hyperbaric bupivacaine 0.5% + 0.8 ml of normal saline intrathecally. The drugs were prepared by one of the authors who did not take further part in the study. An experienced anesthesiologist, who did not participate in the study, performed the SAB and was blinded to the study drug used. Both patients and observers, who recorded and analyzed the data, were blinded to the study drug received.

Patients with a history of adverse response to bupivacaine or nalbuphine, pregnant patients, patients receiving phenothiazine, other tranquilizers, hypnotics or other central nervous system depressants (including alcohol) or suffering from peripheral or central neurological, cardiac, respiratory, hepatic, renal disease; or with body weight more than 100 kg or less than 40 kg and height less than 145 cm or more than 160 cm; and patients having contraindication to SAB were excluded from study.

All the patients fasted for at least 6 h before the procedure. After securing intravenous (18G) access in dorsum of the left hand and attaching routine monitors, preloading with Ringer's lactate solution 15 ml/kg over 10 min was done. SAB was performed with the study drug injected in L3/4 or L4/5 intervertebral space, using a 25-G Quincke spinal needle, in the lateral position, maintaining aseptic precautions, according to the standard institutional protocol. Thereafter, patients were placed in the supine or lateral position for surgery. Intraoperative fluid replacements were given as necessary depending on the blood loss and hemodynamic parameters. Intraoperative hypotension and bradycardia was managed with colloids and atropine 0.6 mg, respectively. In case of any respiratory depression, oxygen through facemask at 6l was administered. Advanced equipment and drugs for resuscitation, airway management and ventilation were kept ready.

The onset of sensory blockade (time taken from the end of injection to loss of pin prick sensation at T_6dermatome) and complete motor blockade (time taken from the end of injection to development of grade 3 motor block, modified Bromage's criteria[5]), highest level of sensory blockade, Intraoperative sedation scores (defined by Ramsay sedation score[6]) duration of sensory blockade (regression to S1 from highest level of sensory blockade), duration of motor blockade (time required for motor blockade return to Bromage's grade I from the time of onset of motor blockade) and duration of effective analgesia (time from the intrathecal injection to the first analgesic requirement, visual analogue scale [VAS] score 4 or more) were recorded.

The changes in pulse rate, systolic and diastolic blood pressure, oxygen saturation (SpO_2) and respiratory rate were recorded at 0, 2, 5, 10, and 15 mins and then at 15-min intervals up to 300 min after SAB, or up to the end point of study. Any side effects in the form of postoperative hypotension, bradycardia, respiratory depression (judged by respiratory rate less than 10 or SpO_2 <90%), nausea and vomiting (in presence of stable hemodynamic parameters) and pruritus were recorded. Those patients who did not develop sensory block up to T_6 and Grade 3 motor block were excluded from the study.

Intensity of pain was assessed by VAS[7] at 0, 10, 15, 30, and 60 min and then at 30-min intervals till 300 min after injection or until the patient received a rescue analgesic. Patients reporting a VAS score 4 or more received rescue analgesics in the form of injection (Inj) Diclofenac 75 mg IM. Incidence of nausea, vomiting and pruritus was noted. Nausea and vomiting was treated with Inj Ondansetron 4 mg i.v. and pruritus with ANTI-HISTAMINICS.

Statistical analysis

Patient characteristic data was analyzed with the Student's *t*-test and Mann–Whitney U test. All values will be expressed as mean ± the standard deviation and a P value less than 0.05 were considered to be statistically significant.

Results

Demographic data

Both the groups were comparable in various demographic data like age, height, weight, gender, and also regarding ASA class distribution. There was no significant difference found in surgical time between the two groups [Table 1].

Study parameters

Table 1 shows that there was significant difference ($P < 0.001$) between mean time for complete sensory block in group 1 and group 2. The mean time for complete motor block in group 1 and group 2 did not show any statistical significance. However, mean duration of analgesia and the time taken for sensory regression to S1 in group 1 and group 2 showed significant difference ($P < 0.001$). Group 1 showed a significantly higher median Ramsay sedation score than group 2 ($P < 0.001$) [Table 2].

Adverse effects

None of our patients had any significant side effects like respiratory depression; two patients were noted to have pruritus

Table 1: Demographic data

	Group 1	Group 2	*P*
Age (yrs)	43.57±8.94	42±9.38	0.5096
Height (cm)	158.4±6.92	159.2±7.29	0.6645
Weight (kg)	58.23±9.68	59.27±6.98	0.6372
ASA Grade 1:2	25:5	26:4	0.7870
Sex (M:F Ratio)	24:6	25:5	0.6872
Surgical time (min)	89±38.17	102±40.82	0.2077

in the study group. Three patients in the study group and two patients in the control group had PONV [Table 3].

Discussion

Intrathecal opioids are used as adjuncts are capable of producing analgesia of prolonged duration but allow early ambulation of patients because of their sympathetic and motor nerve-sparing activities.[8,9] The popularity of Intrathecal opioids (ITO) was undermined by reports of side effects, such as respiratory depression, pruritus, and postoperative nausea and vomiting.[10] Nalbuphine is an opioid (393Da) structurally related to oxy-morphone. It is a highly lipid-soluble opioid with an agonist action at the k opioid receptor and an antagonist activity at the mu opioid receptor.[11,12] Nalbuphine and other k agonists had provided reasonably potent analgesia in certain models of visceral nociception. They have a short duration of action, consistent with their lipid solubility and rapid clearance compared with other opioids like morphine. Recent reports suggest that the safety of ITO is more assured than previously published studies.[13] Nalbuphine given systemically has a reduced incidence of respiratory depression and has been used to antagonize the side effects of spinal opiates.[14,15] There are a few studies of neuraxial administration of nalbuphine that have shown to produce a significant analgesia accompanied by minimal pruritus and respiratory depression.[2]

Yoon *et al*. studied 60 obstetric patients scheduled for caesarean section under SAB to receive morphine 0.1 mg or nalbuphine 1 mg or morphine 0.1 mg with nalbuphine 1 mg in addition to 0.5% bupivacaine 10 mg, and concluded that effective analgesia was prolonged in the morphine group and morphine with nalbuphine group. They found that the incidence of pruritus was significantly lower in the nalbuphine group, while the incidence of nausea and vomiting did not differ in the different groups.[16]

Fournier *et al*. studied the analgesic effects of intrathecal morphine 160 mcg and nalbuphine 400 mcg in geriatric patients scheduled for elective total hip replacement under continuous spinal anesthesia, given in the postoperative period, in the recovery room, and concluded that administration of intrathecal nalbuphine resulted in a significantly faster onset of pain relief and shorter duration of analgesia than intrathecal morphine.[2]

Culebras *et al*. studied intrathecal doses of nalbuphine of 0.2, 0.8, and 1.6 mg in 90 patients and found 0.8 mg to be the most effective dose.[3] In our study, we have used 0.8 mg of nalbuphine as adjuvant for its postoperative analgesic effect over using bupivacaine alone.

In 2011, Mukherjee *et al*. formulated a study to determine whether nalbuphine prolongs analgesia by comparing with control and to find out the optimum dose of intrathecal nalbuphine by comparing the 0.2, 0.4, and 0.8mg doses, which prolonged postoperative analgesia without increased side effects. It was observed that effective analgesia increased with increase in concentration and the ultimate observation of prolongation of analgesia was with 0.4 mg of nalbuphine with 0.5% hyperbaric bupivacaine without any side effects.[17]

In contrast to our study, Tiwari *et al*. in their study have shown that onset of sensory and motor blockade was not affected by adding nalbuphine intrathecally. Seventy-five patients posted for lower limb and lower abdominal surgeries received either 0.2 mg or 0.4 mg nalbuphine or plain bupivacaine intrathecally. This disparity in the onset of blockade could be related to lower dose of nalbuphine used in this study.[18]

Our results showed that onset of sensory block took longer to occur. (544 ± 46.43 sec) in comparison to bupivacaine alone (390.67 ± 64.05 sec). No significant difference was found in terms of onset of motor block. There was no significant difference in the hemodynamic and vital parameters observed between the two groups, which were in accordance to all the previous studies.

We observed that postoperative regression of sensory block to S1 dermatome was significantly slower in the study group. It was also found that the duration of postoperative analgesia was significantly higher in the study group (303.5 ± 18.34 min) in comparison to the control group (209 ± 45.81 min).

None of our patients had any significant side effects like respiratory depression; two patients were noted to have pruritus in the study group. Three patients in the study group and two patients in the control group had PONV.

There are safety issues regarding the intrathecal use of nalbuphine and insufficient data to guarantee safe intrathecal use in human patients. There was an animal study by Rawal *et al*. that examined the effects of nalbuphine in a

Table 2: Study parameters

	Group 1	Group 2	*t* value	*P*
Time for max sensory level T6 (s)	544±46.43	390.67±64.05	10.6161	0.0001
Time for Bromage 3 (s)	266.67±44.52	256.67±42.05	0.8944	0.3748
Duration of Analgesia (min)	303.5±18.34	209±45.81	10.4894	0.0001
Regression to S1 (min)	336.5±17.77	260.5±25.17	13.5105	0.0001
Regression to Bromage 1 (min)	140±30.62	144±18.66	0.8864	0.5184
Mean Ramsay sedation score	3	2		<0.001

Table 3: Adverse effects

	Group 1	Age (%)	Group 2	Percentage
Nausea	2/30	6.66	2/30	6.66
Vomiting	1/30	3.33	0/30	0
Pruritus	2/30	6.66	0/30	0
Urinary retention	1/30	3.33	2/30	6.66

dose of 0.75 mg/kg and reported no behavioral or systematic histopathologic abnormalities.[19] Neuraxial use of nalbuphine is in modern anesthesia practice for more than 15 years. We are not aware of any reports of neurotoxicity of intrathecal nalbuphine since then. The FDA in 2005 advised that nalbuphine may be used during labor and delivery only if clearly indicated, and if, the potential benefit outweighs the risk. We are unaware of any definite caution in the use of nalbuphine by any statutory authority in non-pregnant patients and in subjects more than 18 years of age. We have excluded pregnant patients from our study and obtained clearance from the institutional ethical committee.

Conclusion

Intrathecal nalbuphine prolongs the duration of postoperative analgesia when used as an adjunct, and 0.8 mg is the most effective dose that prolongs early postoperative analgesia without increasing the risk of side effects. We recommend 0.8 mg as the optimal dose of nalbuphine if used intrathecally along with 0.5% hyperbaric bupivacaine for SAB in patients undergoing lower abdominal and lower limb orthopedic surgeries.

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Conflicts of interest

There are no conflicts of interest.

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