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# A COMPARATIVE STUDY TO EVALUATE EFFICACY OF ADMINISTRATION OF NALBUPHINE AS ADJUVANT TO HYPERBARIC BUPIVACAINE INTRATHECALLY IN LOWER LIMB SURGERIES

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**ABSTRACT** Background and aims: Unilateral spinal anesthesia is preferred for surgery limited to one lower limb but the duration of action is short. This randomized study was aimed to evaluate the efficacy of intrathecal nalbuphine for prolonging duration of spinal anesthesia. Material and methods: A total of 60 patients with American society of Anesthesiologist (ASA) physical status I and II, aged 25-35 years, scheduled for elective lower limb orthopedic surgery under spinal anesthesia were randomly allocated into two groups of 30 patients each; Group N (receiving 0.5% hyperbaric bupivacaine 10mg with Inj. Nalbuphine 40 ug in 0.5 ml NS) and Group C (receiving 0.5% hyperbaric bupivacaine 10mg with 0.5ml NS). Both the groups were compared for onset and duration of blockade, duration of analgesia and incidence of block unilaterality. Results: Among the groups, patients' demographic profile, onset of sensory level up to T12 (P value >0.05) and difference between time for achieving complete motor block was comparable. The difference in time to regression of block to L2 was highly significant, (P value < 0.0001). In group N there was prolonged duration of motor block (P value<0.0001) and analgesia (P value < 0.0001) than group C. Campbell sedation score was 1 in group N and 0 in group C (P value = 0.3176 ). The incidence of block unilaterality was comparable: group N (76%) and group C (74%) [P value 0.8592]. Conclusion: Nalbuphine with bupivacaine in unilateral spinal anesthesia provides predominant unilaterality, enhanced postoperative analgesia, stable hemodynamics and minimal side effects.

**KEYWORDS :**

## INTRODUCTION :

Subarachnoid block with bupivacaine is commonly used and effective technique for producing anesthesia and early postoperative analgesia in patients undergoing lower limb orthopedic surgery. [1] When the surgery is limited to only one lower limb unilateral spinal anesthesia is better as it minimizes hemodynamic instability due to restricting sympathetic block to operating side only and avoids motor block to the non operating limb, facilitating early ambulation.[2] Minimal hemodynamic effects, makes unilateral spinal anesthesia suitable for patients having cardiovascular risk factors. [3]

Stress due to surgery highest during the post operative period having major effects on all body parts. Hence pain and stress free post operative period is very essential for reducing morbidity. Hence intrathecal opioids are widely used for superior quality of analgesia as these two types of drugs acts on two different sites, local anesthetic agents act on nerve axon and opioids on the receptor in spinal cord.

Different adjuvants have been used intrathecally with local anesthetic to prolong post operative analgesia with variable effects , which are associated with their own side effects.[4,5] Nalbuphine , a mixed opioid agonist antagonist , had agonist action on kappa receptors and antagonist action on mu- receptors. Hence , while providing analgesia by binding avidly to kappa receptors it also simultaneously lessen the side effects related to mu- opioids.[5]

We hypothesized that administering Nalbuphine intrathecally with hyperbaric bupivacaine will enhance the efficacy of unilateral spinal anesthesia with minimal side effects. The primary aim of our study was to evaluate the efficacy of intrathecal Nalbuphine in prolonging the duration of post operative analgesia and to evaluate the block characteristics . Secondary outcomes include incidence of unilaterality of block, patients satisfaction and incidence of complications.

## MATERIALS AND METHODS:

After obtaining approval from Institutional ethical committee, all patients who were scheduled to undergo elective lower limb surgeries, received information about the study and patients who accepted to participate were enrolled for the study. Inclusion criteria were patients with American Society of Anaesthesiologists (ASA) physical status I and II, aged 18 to 35 years and with BMI between18-35. Patients with bleeding diathesis or coagulopathy, infection at the site of injection, alcoholic or drug abuse, renal impairment, patient with ASA physical status above II, body mass index > 35 and local anesthetic sensitivity were excluded from study. They were assigned to either group N or the group C (1:1 allocation), on the basis of computer generated randomization list. Group N received 2ml of 0.5% hyperbaric bupivacaine plus 40 ug of Nalbuphine in 0.5 ml NS and Group C received 2ml of 0.5% hyperbaric bupivacaine plus 0.5ml NS intrathecally.

A written informed consent was taken from the patients willing to participate in the study. All the patients were taught about Visual Analogue Scale (VAS) for pain assessment . In the operating room, standard monitors were applied and an intravenous line was secured. On arrival to the OT, patient's baseline heart rate (HR), electrocardiogram (ECG), saturation ( SpO2) and non-invasive blood pressure(NIBP) were recorded. Preloading was done with 15ml/kg of lactated Ringer's solution. Under all aseptic precautions subarachnoid block was administered with 25G Quincke needle via midline approach in sitting position. Drug was injected in L3-L4 space over 30 sec and patient was made to lie down in lateral position for 20 min . The lateral position right or left was given with the operative side downwards planned for surgery. An experienced anaesthesiologist, who was unaware of the drug given, evaluated the spinal block and other physiological parameters. HR and NIBP were recorded initially, then every 2.5 minutes for 15 minutes after SAB, then at 15 minutes interval for 1 hour and then hourly for next 6 hours. Hypotension (systolic blood pressure below 90 mmHg or a fall in blood pressure by more than 20% of the baseline value) was treated with additional boluses of intravenous fluids. Intravenous increments of 5mg ephederine was administered if hypotension persisted. Bradycardia (heart rate less than 50 beats per minute) was treated with 0.6mg of intravenous atropine. The onset and duration of sensory block, was assessed by loss of pinprick sensation to 23G hypodermic needle. Dermatomal level was tested every 2 minutes after SAB until level was stabilized for 4 consecutive readings. Also level was tested every 15 minutes till regression by two segments from the highest level (Two segment regression) was noted. The onset and duration of motor block, was assessed initially, then every 5 minutes for 20 minutes following SAB and then every 30 minutes till full recovery using modified Bromage criteria (0: No motor block, 1: Inability to raise extended leg; able to move knees and feet, 2: Inability to raise extended leg and move knee; able to move feet, 3: Complete block of motor limb). The duration of motor block was defined as the time interval between completion of injection and complete recovery of motor power.

Sedation was scored using Campbell score every 5 minutes after SAB for 2 hours (0: Wide awake. 1: Sleeping comfortably but responding to verbal commands. 2: Deep sleep but arousable. 3: Not arousable.).[6]

Postoperatively, pain scores was recorded using VAS, after shifting the patient to PACU-initially every 30 minutes for 2 hours, then every 2 hours for next 8 hours and then after every 4 hours till 24 hours. Duration of effective analgesia was defined as time from intrathecal injection to first analgesic demand postoperatively or VAS > 5 whichever is first, at which a patient received diclofenac sodium i/m 75mg as a rescue analgesic. Patients was observed for any side effects. Episodes of nausea, vomiting, pruritus or shivering during postoperative period (within 24 hours) was recorded. Injection Ondansetron 0.1mg $kg^{-1}$ intravenously was used to treat vomiting. Injection pheniramine maleate 25mg intravenously was used to treat itching. The presence of post dural puncture headache (PDPH), urinary retention and backache were also recorded till 24 hours.

Both the groups will be compared with respect to :
a. Onset of sensory block .
b. Onset of motor block.
c. Duration of sensory block.
d. Duration of motor block.
e. Duration of analgesia.
f. Occurrence of adverse effects.

**RESULTS :**

All the sixty patients completed the study. In both the groups, patients demographic profile was comparable with regard to age, sex, ASA status and BMI [Table 1]. Also surgical time was comparable in both the groups.

Sensory and motor block assessments are summarized in [ Table 2]. Time to reach sensory level upto $T_{12}$ was comparable in both the groups , p value >0.05 . The difference in time to regression of block to $L_2$ was highly significant, p value < 0.0001. On comparison of motor block , difference between time for achieving complete motor block in both the groups were comparable but the difference in duration of motor block was highly significant in group N , p value <0.0001. The duration of analgesia in group N was significantly prolonged as compared to group C, the difference was statistically highly significant , p value < 0.0001.

On comparing the adverse effects , like [ Table 3] hypotension, bradycardia, nausea , vomiting, respiratory depression, pruritus, shivering , no significant difference was observed [ Table 3] .Degree of sedation was 1 in group N as that with group C with the use of Campbell sedation score. P value was 0.3176 , not significant . The frequency of unilaterality of block was 76% with group N and 74% with group C . P value calculated was 0.8592.

**DISCUSSION :**

The result of the current study demonstrated that addition of intrathecal nalbuphine as an adjuvant to hyperbaric bupivacaine prolongs the duration of sensory blockade and post operative analgesia in patients undergoing lower limb surgery without any compilations . However , the addition of nalbuphine to hyperbaric bupivacaine 7.5mg increased the rate of unilaterality of block with minimal changes in hemodynamic parameters.

This prospective study was conducted for patients undergoing below knee surgery under unilateral spinal anesthesia. An exclusively unilateral block only affects the motor, sensory and sympathetic function on one side of the body and hence , offers the advantage of more stable hemodynamic status .[2,3,6] It has reported that with the use of unilateral spinal anaesthesia risk of hypotension was reduced upto four fold. This makes it more suitable for patients with cardiovascular risk factors like with low ejection fraction and coronary artery disease.[7] Also the incidence of urinary retention is very low with unilateral spinal anaesthesia hence , patients are eligible for home discharge sooner as compared to bilateral spinal anaesthesia.[8,9] Most crucial factor for unilaterality of the block is reduction in dose of local anaesthetic agent. But too smaller dose will increase the failure rate of spinal and also shorten the duration of analgesia.[8,10] HM Atef et al., concluded that 7.5mg of hyperbaric 0.5% bupivacaine was the required dose for adequate unilateral spinal anesthesia .[10] Hence, we decided to use the similar dose of bupivacaine and also used adjuvant nalbuphine to enhance postoperative analgesia.

Various adjuvants are used intrathecally or intravenously for prolongation of regional blockade of which opioids are the most popular. But the main obstacles for its use are their side effects. Hence the use of nalbuphine , a mixed opioid agonist antagonist is proved to be beneficial which is mainly synthesized to produce analgesia without undesirable side effects . Nalbuphine binds readily to both mu and kappa receptors. But binding to mu receptors only serves to competitively displace other mu agonists from receptors , without displaying any agonist activity. While it has agonist activity at kappa receptors which are located in brain and spinal cord, involved in nociception. [11,12] Also it is highly lipid soluble hence having rapid clearance compared to morphine.[13] Systemically given nalbuphine found to be effective in reducing incidence of respiratory depression as well as antagonizes the side effects of spinal opiates. [13]

There are few studies ,demonstrated the neuraxial administration of nalbuphine has minimal side effects such as respiratory depression, pruritus, nausea, vomiting and it significantly prolonged the duration of analgesia. Mukherjee et al., studied different doses of intrathecal nalbuphine with hyperbaric bupivacaine in lower limb orthopaedic surgery and concluded that 0.4mg is the most effective dose which prolongs early postoperative analgesia without any significant side effects. [14] In contrast to this ,a study conducted by S Kumaresan et al., demonstrated that 0.6 mg intrathecal nalbuphine as an adjuvant to bupivacaine is the most effective dose for lower limb orthopaedic surgery. [15] Fareed Ahmed et al., also compared the three different doses of nalbuphine in abdominal hysterectomy and showed that 1.6mg nalbuphine when added intrathecally to bupivacaine gives the best results.[16] Since Nalbuphine is mixed agonist antagonist, it exhibit ceiling effect to analgesia that is increasing doses of drug increases analgesia only upto certain point. Beyond this no change in intensity of analgesia is seen. Our study was conducted under unilateral spinal anesthesia hence we decided to use minimal most effective dose of intrathecal nalbuphine i.e. 0.4mg.

The onset of block, both motor and sensory was not affected by adding nalbuphine.[17] In contrast to this finding Sneha Shakooh et al., and Xavier et al., showed that significantly faster onset of sensory and motor block in nalbuphine group. [17,18] This difference may be due to lower dose of nalbuphine used in previous study.[17]

There are various studies reporting intrathecal use of nalbuphine with different doses in bilateral spinal anaesthesia. In our study , we observed that duration of sensory as well as motor block was significantly longer in nalbuphine group. In concurrent to this finding Jaideep Singh et al ., and Fareed Ahmed et al., found that duration of sensory block was significantly extended in nalbuphine group but without prolongation of motor bock. [16,19]

In our study, VAS was significantly lower with nalbuphine group as compared to control group. We also observed that postoperative analgesia was significantly prolonged in nalbuphine group. Our study results are in accordance with the previous studies. [14-19]

The incidence of hypotension, bradycardia, pruritus, nausea, vomiting, respiratory depression was not noted in both the groups. Also the sedation score was comparable in both the groups. These findings were confirmed with the previous studies.[18,19,20] Since respiratory depression is mainly due to mu receptor mediated and as Nalbuphine is mu receptor antagonist, respiratory depression is attenuated. Even with dose upto 2.4 mg of Nalbuphine, respiratory depression is not seen. Culebras et al., conducted study in patients with cesarean section, reported no difference with respect to maternal oxygenation, apgar score and there were no cases of newborn respiratory depression[21]. Hence along with potent analgesic , less respiratory depression with good hemodynamic stability , because of its mu antagonist activity incidents of pruritus and shivering was also significantly lower in nalbuphine group. Again in contrast to other centrally acting opiods nalbuphine has very low abuse potential.[13] None of the patient in our study reported neurotoxicity with the use of intrathecal nalbuphine. In previous studies nalbuphine was also administered intrathecally in pregnant patients without any adverse effects both in mother and fetus.[19]

There are certain limitations to our study. We conducted this study only on ASA I and ASA ll group of patients. Second , the sample was taken was small. The dose of nalbuphine chosen for study was fixed i.e . 0.4 . Though our study confirms 0.4 is the most effective dose further studies are suggested for comparing different doses with larger sample

size including ASA III and ASA IV group.

Thus, it is concluded that adding 0.4mg nalbuphine to 0.5% hyperbaric bupivacaine 7.5 mg for unilateral spinal anaesthesia prolongs both sensory and motor block along with longer lasting postoperative analgesia without any side effects.

## RESULTS:

### 1.Demographic profile :

| | Group C (n=30) | Group N (n=30) | P value |
|---|---|---|---|
| Age (years) | 26 | 24 | NS |
| Sex (male/female ) | 19/11 | 21/9 | NS |
| BMI (mean)(kg/m$^2$) | 25.9 | 26.1 | NS |
| ASA (I /II) | 22/8 | 21/9 | NS |
| Surgical time | 53 +/- 5.2 | 53.2+/-4.8 | NS |

### 2.Block characteristic:

| | Group C (n=30) | Group N (n=30) | P value |
|---|---|---|---|
| Time to achieve sensory block upto $T_{12}$(min) | 9.50+/- 1.76 | 9.42+/-1.82 | 0.8632 |
| Time to regression to level $L_2$(min) | 126 +/- 16.02 | 190+/- 16.62 | <0.0001 |
| Time to achieve complete motor block (min) | 8.62+/- 1.82 | 8.56+/- 1.61 | 0.8929 |
| Duration of motor blockade | 174.78+/- 11.32 | 197.21+/- 13.48 | <0.0001 |
| Duration of effective analgesia (min) | 221.52 +/-26.42 | 326.32 +/- 28.51 | <0.0001 |

### 3.Adverse effects :

| Number of patients | Group C (n=30) | Group N ( n=30) | P value |
|---|---|---|---|
| Hypotension | 0 | 0 | |
| Bradycardia | 0 | 0 | |
| Nausea and vomiting | 2 | 1 | 0.5571 |
| Pruritus | 0 | 0 | |
| Respiratory depression | 0 | 0 | |
| Shivering | 1 | 0 | 0.3176 |

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