

# Optimal dose of intrathecal nalbuphine for prevention of adverse effects related to intrathecal morphine in patients undergoing lower abdominal and lower limb surgeries under bupivacaine spinal anaesthesia: A randomized controlled trial

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## Abstract

**Background:** Prolonged post-operative analgesic effect of intrathecal morphine is often limited by its adverse effects. This study was conducted to know the effect of three different doses of intrathecal nalbuphine in reducing adverse effects related with intrathecal morphine.

**Methods:** The study was performed in a prospective, randomized, observer-blind manner. Total of 120 patients were divided randomly into four groups (n=30) to receive 100 micrograms of morphine alone (Group A), 0.5mg(Group B), 1.0mg(Group C), 1.5mg(Group D) of nalbuphine with 100 micrograms morphine. Post operatively patients were monitored for vital signs, SpO<sub>2</sub>, sedation, pain (VAS), presence of pruritus, nausea and vomiting, respiratory depression and urinary retention for 24 hours.

**Results:** Addition of nalbuphine decreases pruritus, nausea and vomiting in dose dependent manner with maximum effect at 1.5mg. No significant differences observed in vital signs, SpO<sub>2</sub>, sedation score, pain (VAS) score, duration of analgesia and total dose of analgesia required. None of the patients developed respiratory depression and urinary retention.

**Conclusion:** Present study provides evidence that addition of 1.5mg of intrathecal nalbuphine with 100micrograms of intrathecal morphine completely abolishes opioid induced pruritus and significantly reduces nausea and vomiting without reducing analgesic effect of morphine.

**Key words:** Spinal anaesthesia, Morphine, Nalbuphine, Postoperative nausea and vomiting, Pruritus.

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## Introduction

Intrathecal opioids are one of the commonly used adjuncts with local anaesthetics to provide intraoperative and postoperative analgesia. Single dose intrathecal morphine provides prolonged post-operative pain relief lasting up to 24 hours without or with minimal rescue analgesics<sup>1</sup>. Analgesia produced by morphine is mainly mediated by its action through mu ( $\mu_1$  and  $\mu_2$ ) receptors in spinal cord. None of the other commonly used intrathecal opioid or any of the other adjuvant provide analgesia lasting up to 24 hours after single intrathecal dose. Usefulness of this unique property of intrathecal morphine is however limited by commonly associated side effects such as pruritus, nausea, vomiting, sedation, urinary retention<sup>2</sup> and delayed respiratory depression leading to patient discomfort and prolonged hospital stay.<sup>3</sup>

The incidence of pruritus was significantly increased with intrathecal morphine which ranges from 30 – 100% in contrast to only 3% in patients who did

not receive morphine. It is the most common side effect related to the intrathecal administration of opioids.<sup>4</sup> Pruritus actually occurs more commonly after intrathecal opioid administration than after intravenous opioid administration and is not dependent on the type or dose of opioid administered. The mechanism of pruritus is unclear but is likely related to the central mu ( $\mu$ ) opioid receptor activation rather than histamine release because naloxone, naltrexone or the partial agonist nalbuphine are found to be effective in treatment of pruritus. Among the opioids commonly added to intrathecal local anaesthetics, morphine administration has the most frequent risk of nausea or vomiting, whereas fentanyl and sufentanil carry the least frequent risk.<sup>5</sup> There are multiple possible mechanisms that contribute to nausea and vomiting in the setting of neuraxial anesthesia which include delta( $\delta$ ) opioid receptor stimulation in the chemoreceptive trigger zone in the brain, as well as hypotension associated with generalized vasodilation and gastrointestinal hyperperistalsis secondary to unopposed parasympathetic activity. Neuraxial opioid-related nausea and vomiting appears to be dose dependent. Using less than 100 micrograms of morphine reduces the risk of nausea and vomiting, without compromising the analgesic effect.<sup>4</sup> The risk of respiratory depression associated with neuraxial opioids is dose dependent, with a reported frequency that approaches 3% after the administration of 800 micrograms of intrathecal morphine.<sup>6</sup> Respiratory

depression may arise from rostral spread of opioids within the CSF to the chemosensitive respiratory centers in the brainstem.<sup>7</sup> There is a risk of late respiratory depression, occurring as late as 24 hours after injection. The incidence of urinary retention with intrathecal morphine ranges from 63 to 78% which is significantly more compared to other intrathecal opioids.<sup>8</sup> The mechanism of urinary retention is poorly understood. Neuraxial opioids may affect the urinary function by suppressing detrusor contractility and reducing the sensation of urge.<sup>9</sup>

Nalbuphine is a mixed opioid agonist-antagonist. It acts as an agonist at kappa ( $\kappa$ ) opioid receptors and antagonist at mu ( $\mu$ ) opioid receptors. Thus it may attenuate mu-opioid-receptor related side effects of morphine.<sup>10</sup> Since the main analgesic action of morphine is by mu agonism, there is a theoretical possibility of reversing the analgesic properties of morphine when nalbuphine is co-administered.<sup>10</sup> However, studies have shown that nalbuphine administered either intravenously<sup>11</sup> or intrathecally<sup>12</sup> reduced the intrathecal morphine induced side effects without altering analgesic property of morphine. However, optimal intrathecal dose has not been studied. In this study, the effect of three different doses (0.5, 1.0, 1.5 mg) of intrathecal nalbuphine, added to bupivacaine and morphine was compared with control group who received only intrathecal bupivacaine and morphine.

## Materials and Methods

One hundred and twenty patients belonging to American Society of Anesthesiologists (ASA) physical status 1 and 2 between age groups of 18 to 60 years undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia were selected for the study. An informed written consent was obtained from the patients for participation in the study.

### Exclusion criteria:

- Pregnant patients
- Patient's refusal to participate in the study.
- Any contraindication to spinal anaesthesia.
- Any patient with a history of allergy to any of the study drugs.
- History of opioid abuse.
- Impaired renal, hepatic and biliary function.
- Patients on tranquilizers, hypnotics, sedatives & other CNS depressant drugs.
- Patients undergoing day care surgeries.
- Pre induction or per operative urinary bladder catheterization.
- Patients with history of obstructive sleep apnea.
- Failed spinal anaesthesia requiring supplementation with general anaesthesia.

All patients underwent preanaesthetic evaluation with complete history and physical examination.

Laboratory investigations were ordered as per ASA guidelines.

All patients were preloaded with 15ml/kg of crystalloid. Standard monitors which include pulse oximeter, noninvasive blood pressure and five lead electrocardiography were attached. All patients received spinal anaesthesia in sitting position with 25G Whitacre spinal needle in L3-4 space. Patients were divided randomly into four groups using lottery method as Group A, B, C and D of 30 patients in each group and received the drugs as follows

Group A: 0.5% Bupivacaine heavy + 100 micrograms of morphine.

Group B: 0.5% Bupivacaine heavy + 100 micrograms of morphine + 0.5 mg of nalbuphine.

Group C: 0.5% Bupivacaine heavy + 100 micrograms of morphine + 1.0 mg of nalbuphine.

Group D: 0.5% Bupivacaine heavy + 100 micrograms of morphine + 1.5 mg of nalbuphine.

Dose of bupivacaine was decided based on the surgery and patient characteristics. Anesthesiologist who prepares and administers the drug would not be involved in recording the postoperative findings and statistical analysis.

At the end of the surgery, patients were shifted to the post anaesthesia care unit and they were monitored for the next 24 hours for the following:

- Pulse rate and Oxygen saturation using pulse oximeter.
- Non-invasive arterial blood pressure every 2 hours.
- Respiratory rate every 2 hours.
- Pain was assessed using Visual analogue scale (VAS)<sup>13</sup> every 2 hours. Breakthrough pain was managed by inj. Paracetamol 1g IV if VAS score > 4.
- Time to first analgesic requirement.
- Total dose of rescue analgesics given postoperatively.
- Nausea and vomiting was assessed using a 3-point scale<sup>14</sup> (0 = no nausea and vomiting, 1 = mild nausea or vomiting not requiring treatment, 2 = moderate nausea or vomiting requiring treatment and 3 = severe vomiting requiring more than one dose of antiemetic or multiple antiemetics).
- Pruritus was assessed using a 3-point scale (0 = no pruritus, 1 = mild to moderate facial pruritus that may or may not require treatment, 2 = severe facial pruritus requiring treatment, 3 = pruritus involving extra facial region requiring treatment).
- Urinary retention
- Sedation score: Using Ramsay Sedation Scale<sup>15</sup> (1-Patient is anxious and agitated or restless, or both, 2-Patient is co-operative, oriented, and tranquil, 3-Patient responds to commands only, 4-Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5-Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6-Patient exhibits no response)

Adverse effects were managed as follows. Vomiting was treated with 4 mg dexamethasone intravenously. Pruritus was treated with 4 mg of ondansetron intravenously. Urinary retention was managed with warm compresses and urinary catheterization if needed. Respiratory depression evidenced by respiratory rate < 8 breaths/ minute was managed with non-invasive or invasive ventilation appropriate for the patient.

Statistical analysis of the data was done using Chi-square test. The statistical package SPSS version 16 software was used for the analysis. P value <0.05 was considered as significant.

## Observations and Results

There were no significant differences in demographic data which includes age, sex, weight and ASA physical status among the patients between four groups (Table 1). There was no significant difference in total dose of analgesia required and sedation score among the patients between four groups. There were no significant difference in pulse rate, mean arterial blood pressure, respiratory rate, and oxygen saturation (table 2). None of the patients in any of the groups developed respiratory depression and reduction in arterial oxygen saturation and also urinary retention requiring treatment.

**Table 1: Demographic characteristics and ASA physical status comparison**

	Group A n=30	Group B n=30	Group C n=30	Group D n=30	P value
Age	43.07±11.5	39.93±13.9	39.57±13.1	37.87±14.2	0.494NS
Weight	63.37±9.9	63.27±9.3	64.40±6.8	65.67±11.2	0.743NS
Sex					
Males(n)	18	17	22	17	0.493NS
Females(n)	12	13	8	13	
ASA status 1 (n)	22	24	25	25	0.741NS
ASA status 2 (n)	8	6	5	5	

For age and weight the values are as Mean ± Standard deviation. n= number of subjects. NS = not significant

**Table 2: Comparison of vital signs and oxygen saturation**

	Group A n=30	Group B n=30	Group C n=30	Group D n=30	P value
Pulse Rate	73.20±10.4	70.37±7.6	74.23±7.0	71.23±7.4	0.252NS
Mean Arterial Pressure	82.23±10.3	79.87±7.9	78.10±7.6	76.70±6.4	0.062NS
Respiratory Rate	11.50±1.9	10.67±1.9	13.03±2.3	11.77±1.9	0.15NS
SpO <sub>2</sub>	97.57±1.7	97.93±1.5	97.33±1.6	97.70±1.9	0.60NS

Values are as Mean ± Standard deviation. n= number of subjects. SpO<sub>2</sub>= oxygen saturation NS = not significant

The mean maximum VAS score was 1.63 in group D which was significantly lower compared to group A- 2.70 group B- 2.50 group C- 2.53 (Table 3). There was no significant difference in time for first analgesia demand by the patients among four groups.

**Table 3: Comparison of Pain score, Sedation score and Analgesic requirement**

	Group A n=30	Group B n=30	Group C n=30	Group D n=30	P value
VAS Score	2.70±1.4	2.50±1.4	2.53±1.4	1.63±1.2	0.016Sig
Time for first rescue Analgesia	19.10±6.5	19.90±5.6	17.87±5.0	19.20±4.3	0.54NS
Total dose of Paracetamol (gms)	0.93±0.9	0.87±0.8	1.17±0.9	0.90±0.8	0.71NS
Sedation Score	2.60±0.4	2.27±0.5	2.40±0.4	2.53±0.6	2.12NS

Values are as Mean ± Standard deviation. n= number of subjects. VAS = visual analogue scale. NS = not significant

Nausea and vomiting and pruritus were higher in patients who received morphine alone and were significantly more compared to patients who received nalbuphine and morphine. In group A 53.3% of the patients required treatment for vomiting whereas 23.3% in group B, 10% in group C and none of the patients in group D required treatment for the same. This indicates that increasing doses of nalbuphine from 0.5mg to 1.5mg decreases morphine induced nausea and vomiting (Table 5 and 6).

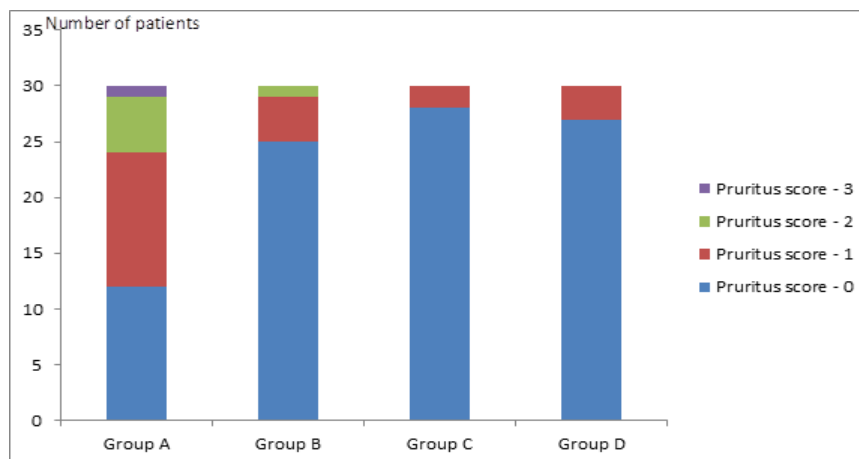
**Table 4: Comparison of Pruritus Score**

Pruritus score †	Group A n=30, (%)	Group B n=30, (%)	Group C n=30, (%)	Group D n=30, (%)
0	12 (40%)	25 (83.3%)	28 (93.3%)	27 (90%)
1	12 (16.7%)	4 (13.3%)	2 (6.7%)	3 (10%)
2	5 (40%)	1 (3.3%)	0 (0%)	0 (0%)
3	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)

$\chi^2=33.503$   $p<0.001$  very highly significant

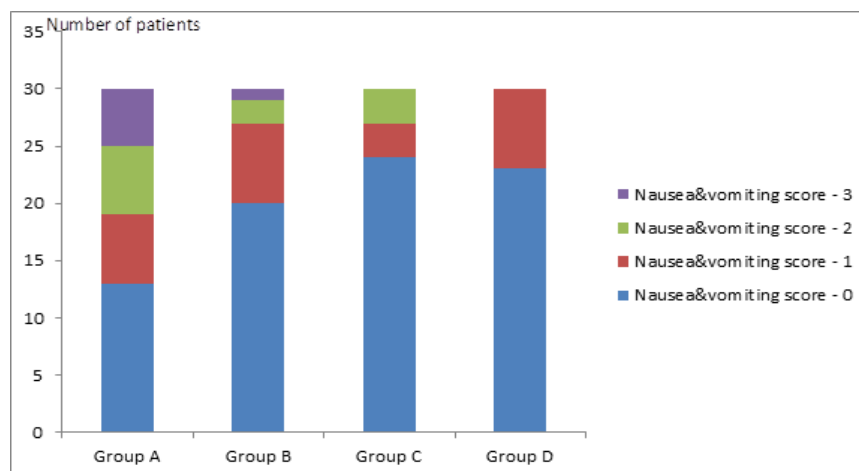
† 0 = no pruritus, 1 = mild to moderate facial pruritus that may not require treatment, and 2 = severe facial pruritus requiring treatment. 3 = pruritus involving extra facial region requiring treatment. N = number of patients.

% = percentage of patients in the group.

**Fig. 1: Comparison of Pruritus score****Table 5: Comparison of nausea and vomiting score**

Nausea & Vomiting Score †	Group A n=30, (%)	Group B n=30, (%)	Group C n=30, (%)	Group D n=30, (%)
0	13 (43.3%)	20 (66.6%)	24 (80%)	23 (76.7%)
1	6 (20%)	7 (23.3%)	3 (10%)	7 (23.3%)
2	6 (20%)	2 (6.7%)	3 (10%)	0 (0%)
3	5 (16.7%)	1 (3.3%)	0 (0%)	0 (0%)

$\chi^2=23.71$   $p=0.005$  highly significant † 0 = no nausea and vomiting, 1 = mild nausea or vomiting not requiring treatment, 2 = moderate nausea or vomiting requiring treatment and 3 = severe vomiting requiring more than one dose of antiemetic or multiple antiemetics. % = percentage of patients in the group.

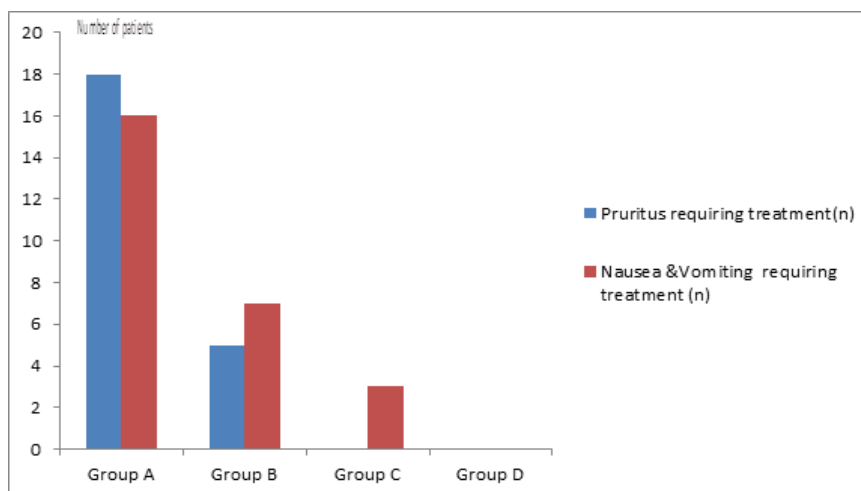
**Fig. 2: Comparison of Nausea & vomiting score**

In group A 60% of the patients required treatment for pruritus whereas 16.7% in group B and none of the patients in group C and group D required treatment for the same. This indicates that increasing doses of nalbuphine from 0.5mg to 1mg and 1.5mg decreases morphine induced pruritus in dose dependent manner (Table 4 and 6).

**Table 6: Number of patients requiring treatment for Pruritus and Nausea & Vomiting**

	Group A n=30, (%)	Group B n=30, (%)	Group C n=30, (%)	Group D n=30, (%)	P value
Pruritus requiring treatment (n)	18 (60%)	5 (16.7%)	0 (0%)	0 (0%)	<0.001 vhs
Nausea & Vomiting requiring treatment (n)	16 (53.3%)	7 (23.3%)	3 (10%)	0 (0%)	<0.001 vhs

n= number of subjects. %=percentage of patients in the group. vhs = very highly significant



**Fig. 3: Number of patients requiring treatment for pruritus and nausea & vomiting**

## Discussion

Prolonged post operative analgesia provided by intrathecal morphine however limited by adverse effects which vary from minor and common side effects like pruritus, vomiting to less common and more severe respiratory depression. This study was conducted to know the effect of adding three different doses of nalbuphine with intrathecal morphine to reduce these adverse effects. In this study it was found that addition of 0.5mg of nalbuphine decreases and addition of 1mg and 1.5mg of nalbuphine completely abolishes pruritus. Similarly nausea and vomiting also significantly reduced by addition of 0.5mg nalbuphine, with the effect increasing with the dose, since none of the patients who received 1.5mg nalbuphine required treatment for nausea and vomiting. Only one study is available in literature which studied the use of intrathecal nalbuphine to reduce side effects related to intrathecal morphine. The study was conducted by Moustafa AM et al<sup>12</sup> in which single dose of nalbuphine (1 mg) was added to intrathecal morphine 200 micrograms with bupivacaine in patients undergoing total knee replacement. The authors concluded that intrathecal addition of nalbuphine to morphine

decreases opioid related pruritus and nausea and vomiting without affecting postoperative analgesia.

Our study included only ASA 1 and 2 non obese patients and with age group of 18 to 65 years without any compromised cardio respiratory diseases. One of the previous study conducted by Rathmall et al<sup>4</sup> showed that the risk of opioid induced respiratory depression in this age group of patients and at dose of less than 800 micrograms, is very low and it is evident in our study since none of the patients in any of the four groups developed respiratory depression.

In our study we found that addition of 1 mg and 1.5 mg of nalbuphine significantly reduces pruritus. One of the similar studies conducted by Charuluxananan S et al<sup>16</sup> showed that even intravenous nalbuphine at a dose of 5mg is more effective than subhypnotic dose (10mg bolus) of propofol in treatment of intrathecal morphine induced pruritus after caesarean delivery.

Wang JJ et al<sup>17</sup> in their study compared nalbuphine versus naloxone for prevention of morphine related adverse effects and found that co administration of either nalbuphine or naloxone with epidural morphine reduces the incidence of morphine-related side effects. However, unlike naloxone, nalbuphine did not attenuate the analgesic effect of epidural morphine.

Liao CC et al<sup>18</sup> compared the Efficacy of intramuscular nalbuphine versus diphenhydramine for the prevention of epidural morphine-induced pruritus after cesarean delivery. Nalbuphine proved to be better than diphenhydramine for prevention of epidural morphine-induced pruritus in patients who underwent cesarean section. Prophylactic intramuscular nalbuphine (10 mg) is effective in decreasing the incidence and severity of pruritus and does not affect analgesia.

Yu-Chang Yeh et al<sup>19</sup> demonstrated that combination of low-dose nalbuphine and morphine in PCA decreases the incidence of opioid-related nausea, without affecting the analgesia and PCA requirement. Yoon et al<sup>20</sup> compared between three groups of patients who received intrathecal (morphine 0.1 mg), (nalbuphine 1 mg) and (morphine 0.1 mg with nalbuphine 1 mg) in addition to 0.5% bupivacaine 10 mg in 60 obstetric patients undergoing cesarean section. They concluded that the duration of effective analgesia was longer with morphine alone and morphine added to nalbuphine than in nalbuphine alone group. The incidence of pruritus was significantly higher in morphine alone group while nausea and vomiting were the same in all groups.

Our study shown that addition of 0.5mg and 1mg nalbuphine had no effect on duration of analgesia produced by morphine with VAS score comparable with morphine alone. Patients who received 1.5mg of nalbuphine had significantly low VAS score in first 24 hours. However total dose of analgesia required in first 24 hours and time for first analgesia demand by the patients are similar in all four groups. Fareed Ahmed et al<sup>21</sup> studied the effect of intrathecal nalbuphine at three different doses of 0.8, 1.6, 2.4mg as adjuvant to 0.5% hyperbaric bupivacaine in patients undergoing total abdominal hysterectomy under subarachnoid block. They concluded that analgesic effect is maximum at dose of 1.6 mg and using 2.4 mg dose does not offer any added advantage regarding the duration of analgesia.

Since we used low dose of morphine none of the patients in our study developed serious complications like respiratory depression. More studies are required to know the effect of intrathecal nalbuphine on these complications. Study conducted by Baxter AD et al<sup>22</sup> showed that intravenous nalbuphine was found to be useful in prevention of epidural morphine-induced respiratory depression.

## Conclusion

Based on our observation we conclude that addition of 0.5, 1 and 1.5 mg of intrathecal nalbuphine with 100 micrograms of intrathecal morphine significantly reduces intrathecal morphine induced pruritus and nausea and vomiting in dose dependent manner with maximum effect at 1.5mg, without reducing analgesic effect of morphine.

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