

## Randomized Double-Blind Trial Comparing Efficacy of Intravenous Nalbuphine vs Intrathecal Nalbuphine for Prevention of Intrathecal Morphine Induced Pruritus in Orthopaedic Surgeries

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Intrathecal morphine provides excellent postoperative pain relief but results in pruritus in 30-60% of patients. Nalbuphine, an opioid agonist-antagonist prevents intrathecal morphine-induced itch when given by intravenous route. In this study, we compared efficacy of intrathecal and intravenous nalbuphine for the prevention of intrathecal morphine-induced pruritus. 90 patients were randomly divided into two groups. IT group received 100 mcg of morphine with 400 mcg of nalbuphine intrathecally. IV group received 100 mcg of morphine intrathecally and 400 mcg of nalbuphine intravenously. Incidence of itching, respiratory depression, hypotension, nausea, vomiting, sedation and analgesia were compared between the groups every 4<sup>th</sup> hourly for 24 hours. Data were analyzed with Chi-square test and Mann-Whitney test. Incidence of itching in 24 hours period was 11.6% (5 patients) in IV group and 4.8% (2 patients) in IT group which was comparable. (P= 0.250) Two patients in IV group had intractable itching requiring naloxone. Incidence of itching at all time intervals was comparable between the groups. Analgesia was prolonged in IV group (P=0.03) Incidence of nausea, vomiting, sedation and respiratory depression was comparable. We conclude that intrathecal nalbuphine and intravenous nalbuphine were equally effective in preventing intrathecal morphine induced pruritus. The duration of analgesia was more when nalbuphine was given by IV route as compared to IT route.

**Keywords:** Postoperative pain, intrathecal morphine, nalbuphine, pruritus

### Introduction

Orthopaedic surgeries are associated with high postoperative pain scores in first 24 hours post-operatively, resulting in increased analgesic demand.<sup>1</sup> Low-dose intrathecal (IT) morphine provides excellent pain relief for orthopaedic surgeries in the first 48 hours with beneficial effects lasting up to one week.<sup>2</sup> Pruritus is the most commonly reported adverse effect of IT morphine which is seen in 30-60% of patients undergoing orthopaedic surgeries and has been noticed

even at lower doses.<sup>3</sup> The exact mechanism of pruritus induced by IT morphine is not clear and many mechanisms like cephalad migration of morphine towards the itch centre in the central nervous system (CNS), antagonism of inhibitory transmitters and modulation of serotonergic pathway are involved.<sup>3,4</sup>

Nalbuphine, an opioid agonist antagonist can suppress itch by its antagonist action on  $\mu$  opioid receptors and agonist action on spinal kappa opioid receptors. Nalbuphine is superior to all other pharmacological agents and has been suggested as the first line of management for IT morphine-induced pruritus.<sup>5</sup> Nalbuphine can interfere with the analgesia produced by pure agonists like morphine due to its antagonist action on  $\mu$  opioid receptors, when both the agents are used together. Previous studies have proven that morphine and nalbuphine admixture given by intravenous (IV) route provides an

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additive effect on analgesia with reduction in pruritus.<sup>5,6</sup> The efficacy of IT nalbuphine for prevention of IT morphine-induced pruritus has not been studied yet.

We hypothesized that IT nalbuphine would be better than IV nalbuphine for the prevention of pruritus as the drug would be deposited near spinal opioid receptors. Studies on efficacy of IT nalbuphine as an antipruritic agent and its effect on analgesia when administered along with IT morphine are not available. The aim of this study was to compare the efficacy of IV nalbuphine against IT nalbuphine for the prevention of IT morphine induced pruritus.

## Methods:

This was a prospective randomized double blinded study conducted over a period of one year, after approval from the institutional ethics committee. The trial was registered with the clinical trial registry of India. (CTRI/2017/04/008332) Patients between 18-60 years of age of the American Society of Anesthesiologist (ASA) with physical status I and II of either sex, posted for elective orthopedic surgeries under subarachnoid block were included in the study. Patients with ASA III and above, psychiatric illness, with lower respiratory tract ailment, on anticoagulants or opioids and with pre-existing dermatological conditions were excluded from the study.

Informed and written consent was obtained preoperatively. Patients were randomly divided into two groups, Group IV and group IT by a computer-generated list of random numbers. Electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximeter (SpO<sub>2</sub>) were connected and monitored continuously throughout the intraoperative period. Subarachnoid block was given using 25G quincke's spinal needle at L2-L3, L3-L4 space in the sitting position

under strict aseptic precautions and optimal positioning. Preservative free morphine sulphate injection (Vermor-10, Verve human care laboratories, India) was diluted using 0.9% normal saline in a 1ml syringe to a volume of 100µg/0.1ml. Nalbuphine hydrochloride – 10mg/ml (NACPHIN -10, Neon laboratories Ltd, India) was diluted using 0.9% normal saline in 1ml syringe (Tuberculin, Dispovan syringe) to a volume of 100µg/0.1 ml. Group IV received 15 mg of bupivacaine (0.5% heavy) with 100µg of morphine (0.1ml) and 0.4ml of 0.9% normal saline, total volume of injectate of 3.5 ml. Group IT received 15mg of 0.5% heavy bupivacaine and 100µg of morphine (0.1ml) with 400µg of nalbuphine (0.4 ml), total volume of injectate of 3.5 ml. Group IV received nalbuphine 4 mg (4 mL) intravenously and group II received 4 mL of normal saline intravenously. Sensory level of analgesia was monitored every two minutes for initial 30 minutes with 26G hypodermic needle. Sedation score was monitored as per Ramsay sedation scale.<sup>7</sup> Heart rate (HR) < 50/min was taken as bradycardia and treated with atropine 0.6 mg IV. Hypotension was defined as fall of 30% from baseline MAP and was treated with IV fluids and vasopressors. Respiratory depression (RD) was defined as SpO<sub>2</sub> < 94% and/or respiratory rate (RR) < 8/minute. RD was treated with supplemental oxygen via facemask. All the patients received prophylactic anti-emetic ondansetron 4mg IV. Post-operatively patients were assessed for every 4th hourly for first 24 hours for incidence of pruritis, nausea, vomiting, pain and respiratory depression. Itching was assessed on 0- 3 scale where 0 is no itching, 1 is mild itching with no skin scratching, 2 is moderate itching with skin scratching and 3 is intolerable itching<sup>8</sup> Score of > 2 was treated with naloxone 0.25 mcg/kg/hr IV infusion. The presence of itching at any time interval was taken as incidence of itching in

24 hours. Verbal rating scale (VRS) of 0-10 was used to assess pain.<sup>9</sup> Diclofenac 1.5 mg/Kg by intramuscular route was given on demand. Time for demand of first rescue analgesic was noted and this duration was taken as duration of analgesia. The total number of analgesics received was noted. The patients with persistent respiratory depression after oxygen supplementation were treated with naloxone 0.04mg/kg IV bolus. Post - operative nausea was assessed by VAS scale of 0-10, where 0 is no nausea and 10 is worst nausea with retching.<sup>10</sup> Vomiting was assessed by the presence or absence of it and the number of episodes. Patients with >1 episode of vomiting were treated with metoclopramide 10mg IV.

The primary outcome of the study was to compare the incidence of pruritus between IV and IT nalbuphine. The secondary outcomes of the study were to compare severity of pruritus, analgesia, incidence of nausea, vomiting, respiratory depression, sedation score, hemodynamic stability, and sensory level of analgesia between the groups.

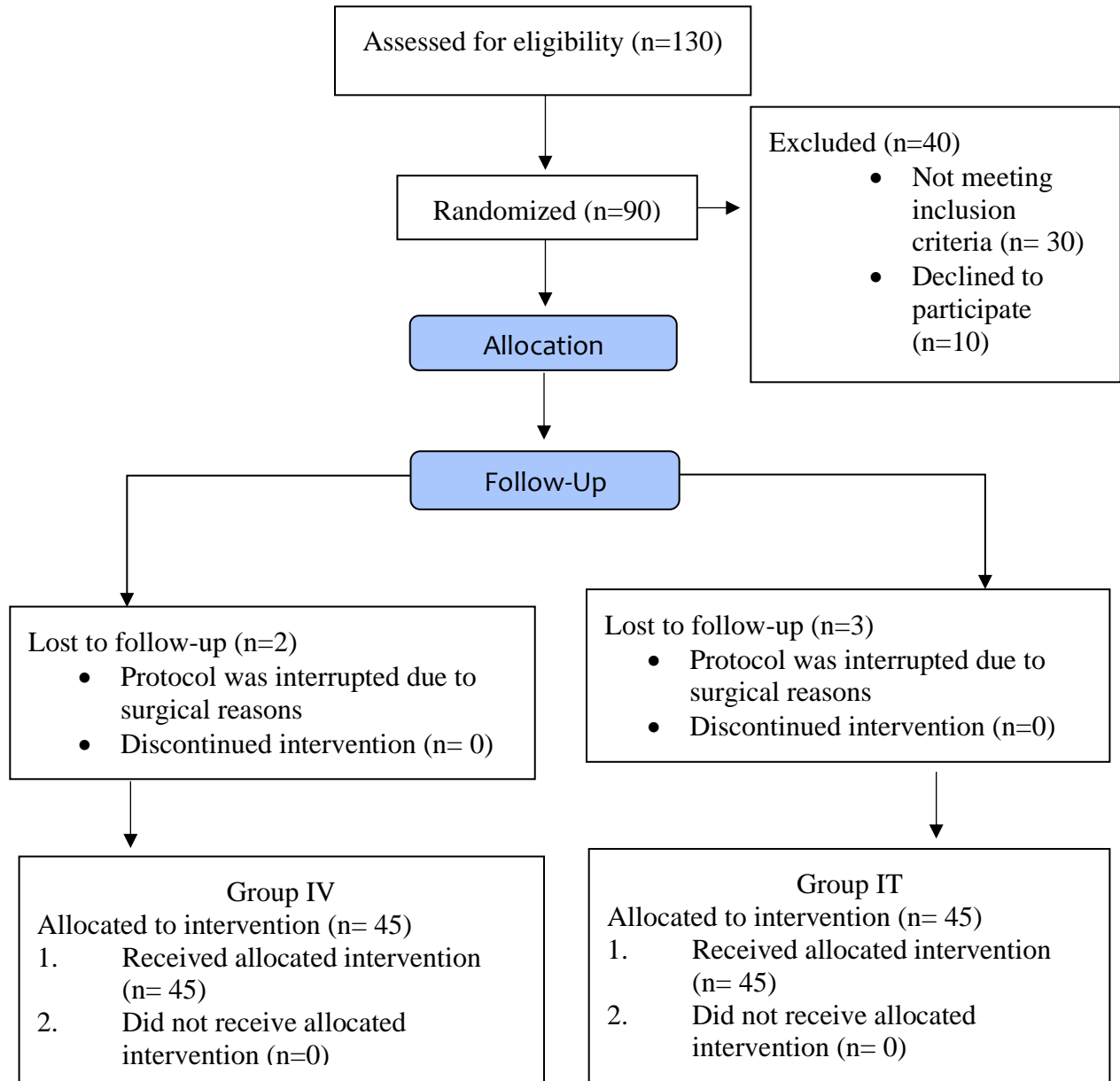
Sample size calculation was done based on previous study with the incidence of pruritus of 50% with IV nalbuphine.<sup>11</sup> Assuming the reduction in incidence of pruritus by 60 % in IT group, sample size of 40 patients per group were needed for significance of 5% and power of study as 80%. 45 patients per group were included to avoid possible dropout. Statistical analysis was done using statistical package for social sciences (SPSS) version 23. Normality of data was assessed with Shapiro Wilk test. Age, duration of surgery, time for maximum sensory level were compared using independent t test and expressed as mean  $\pm$  standard deviation (SD). Incidence of pruritus, nausea, vomiting, respiratory depression, hemodynamic instability was assessed by Chi square test

and results were expressed as number and percentage. Time of first analgesic requirement and total analgesic requirement was compared using the Mann Whitney U test and expressed as median  $\pm$  interquartile range (IQR). P value less than 0.05 was taken as significant for a two-sided test.

## Results

130 patients were assessed for inclusion in the study, 90 patients were included in the study and received intervention (Fig:1) Three patients in IT group and two in IV group were excluded from analysis due to anesthesia and surgery related causes. Remaining 85 patients were analyzed statistically. Patient's characteristics were comparable in both groups. (Table 1). Analgesia was significantly prolonged in IV group with P value of 0.03. Total number of analgesics required was similar in both groups. Incidence of itching in 24 hours period was 11.6% (5 patients) in IV group and 4.8% (2 patients) in IT group which was not statistically significant. (P= 0.250) Two patients IV group had intolerable itching and required naloxone while no patient in IT group had intolerable itching. Incidence of itching at different time intervals was comparable between the groups. (Table 2) The pain scores were comparable between the groups at all time intervals (Table 3). Incidence of nausea/vomiting was comparable between groups. (Table 4) Six patients in IV group and three patients in IT group required antiemetic agent. Respiratory depression was seen in 2 patients in IV group and 5 patients in IT group, which responded to oxygen supplementation. Intraoperative hypotension was relatively more in IT group (42%) as compared to IV group (23%). (P=0.05). Sedation scores were 3 in all the patients in both groups except two patients in IV group, who had a sedation score of 4.

**Figure 1: CONSORT Diagram**



**Table 1: Patient's characteristics**

Parameter	Group IV Mean $\pm$ SD	Group IT Mean $\pm$ SD	P value
Age in years	40.09 $\pm$ 15.24	42.02 $\pm$ 12.21	0.522
Gender(M/F)- number	26/17	24/18	

Duration of surgery(min)	105 ± 40.78	103.85 ± 43.29	0.867
Maximum sensory level (min-max)	T <sub>6</sub> (T <sub>4</sub> -T <sub>8</sub> )	T <sub>6</sub> (T <sub>6</sub> -T <sub>8</sub> )	0.80
Time for maximum sensory level(min)	11± 0.62	10.5 ± 0.86	0.690
Time for first rescue analgesic (min) *	735 (528-1440)	528 (325-1440)	0.032
Total no of rescue analgesics (min-max)	1 ± 1 ( 0-3)	1± 1 (0-2)	0.615

\* median (25<sup>th</sup> -75<sup>th</sup> percentile)

**Table 2:** Incidence of itching at different time intervals

Parameter	Group IV number (%)	Group IT number (%)	P value
4 <sup>th</sup> hour	2 (4.7%)	1 (2.4%)	0.571
8 <sup>th</sup> hour	3 (7 %)	1 (2.4%)	0.371
12 <sup>th</sup> hour	3(7%)	1(2.4%)	0.317
16 <sup>th</sup> hour	2 (4.7%)	0	0.157
20 <sup>th</sup> hour	3 (7%)	0	0.08
24 <sup>th</sup> hour	2 (4.7%)	0	0.157

**Table 3:** Pain scores at different time intervals

Parameter	Group I Median /IQR* (min-max)** *	Group II Median / IQR* (min-max) **	P value
4 <sup>th</sup> hour	0.00/ 0-0 (0-6)	0.00 / 0-0 (0-6)	0.203
8 <sup>th</sup> hour	0.00 /0-6 (0-8)	0.00/ 0-2 (0-6)	0.992
12 <sup>th</sup> hour	0.00/ 0-2 (0-8)	0.00/ 0-2 (0-7)	0.519
16 <sup>th</sup> hour	0.00 / 0-2 (0-8)	0.00/ 0-2 (0-6)	0.553
20 <sup>th</sup> hour	2 / 0-3 (0-8)	0.00 / 0-2 (0-8)	0.147
24 <sup>th</sup> hour	0.00/ 0-2 (0-6)	0.5/ 0-2 ( 0-8)	0.905

\*\* - minimum-maximum pain score

**Table 4:** Incidence of complications

Parameter	Group IV No(%)	Group IT No (%)	P value
Itching	5 (11.6%)	2 (4.8%)	0.250
Nausea	6 (14%)	5 (11.9%)	0.778
Vomiting	9 (20.9%)	5 (11.9%)	0.262
Respiratory depression	2 (4.7%)	5 (11.9%)	0.224
Intraoperative hypotension	10 (22.3%)	18 (42.9%)	0.055

## Discussion

In this study we found that the incidence and severity of itching were comparable between the groups. Incidence of nausea vomiting, respiratory depression, hypotension, and sedation scores were similar between the groups. Time for first rescue analgesic was prolonged with the IV group than the IT.

Yeh et al compared different doses of morphine nalbuphine admixture through patient-controlled analgesia (PCA).<sup>6</sup> The incidence of itching in 24 hours was 3 % with equal doses of morphine and nalbuphine combination and it was zero with higher doses of nalbuphine. In our study 24 hours incidence was 4.8% in IT group and 11.6% in IV group. Cumulative PCA requirements and pain scores were comparable only between the morphine group and morphine nalbuphine admixture group. In our study pain scores and the requirement for rescue analgesics were similar in IT and IV nalbuphine group.

Intrathecal morphine gives dose dependent analgesia by its action on spinal and supraspinal mu receptors. This antinociceptive action of IT morphine can be reversed by IT administration of mu & kappa receptor antagonist.<sup>12</sup> Mohd Salleh et al found incidence of pruritus was 10% with IV nalbuphine and of moderate and severe itching was zero at 24 hours.<sup>13</sup> Somboonviboon et al found that incidence of hypotension after IT morphine was related to sensory level above T4.<sup>14</sup> In our study the maximum sensory level achieved was T<sub>6</sub> in IT group and T<sub>4</sub> in the IV group, but the incidence of hypotension was more in the IT group.

We conclude that intrathecal nalbuphine and intravenous nalbuphine are equally effective in preventing intrathecal morphine induced pruritus. The duration of analgesia is more

when nalbuphine was given by IV route compared to IT route.

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