

# Comparison of Intravenous Ketorolac and Nalbuphine for Post-Operative Analgesia After Orthopedic Surgery

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## ABSTRACT

**Background:** Patients may vary 8 folds in their requirement of analgesics. Sometimes health professionals use inadequate analgesics in fear of its adverse effects like nausea, vomiting, respiratory depression and cost of drugs etc. But it is patients' right to get adequate relief of pain in post operative period. Aim of this study was to identify the effective analgesic for post-operative period in orthopedic surgery by comparing to commonly used analgesic injectable Ketorolac and Nalbuphine.

**Materials and methods:** This study was designed in the year 2009 as a double blind clinical trial to compare the analgesic efficacy of intravenous Ketorolac and Nalbuphine in case of post operative pain management in orthopedic surgery. Sample was selected randomly using the 'Random Number Table and selection criteria. The sample was divided into group A and Group B by lottery method. Drugs allotted for group A was Intravenous Injection Ketorolac (30mg) for group B was Injection Nalbuphine (20mg). Both drugs were applied just after operation and this point was regarded as '0' hour. Drugs were continued as 6 hourly I.V doses and the patients were followed up at 1, 6, 12, 24, 32 and 48 hours. At each time patient was asked to mark their current assessment of pain on both (VAS) and (NRS). At the same time pulse, blood pressure, respiratory rate, and sedation score and any unwanted effects were recorded. Total 132 respondents were included in this study that underwent different types of elective orthopedic surgery.

**Results:** Among the samples 65 (49.24%) were in Group-A and 67 (50.76%) were in Group-B. The average age distribution of this study was  $40.52 \pm 15.03$  years and the age and sex distribution of this study were homogenous. This study revealed that both Ketorolac and Nalbuphine reduced the pain score below '4' within 12 hours and it gradually decreased more. Decrement of pain score with Nalbuphine was significantly better than Ketorolac from 12 hours and onwards. Decrement of pulse rate, blood pressure, respiratory rate and sedation score also statistically favoured Nalbuphine from 6 - 12 hours and onwards. Changes in diastolic blood pressure were proved null with Z-test. No events of respiratory depression, bradycardia or shock were observed in any group.

**Conclusion:** This study clearly concluded that both intravenous Nalbuphine and Ketorolac can be used safely and effectively in management of post operative pain in Orthopedics and intravenous Nalbuphine is superior to intravenous Ketorolac in this regard.

**Key words:** Nalbuphine; Ketorolac; Post-operative pain.

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## INTRODUCTION

Patients may vary 8 folds in their requirement of analgesics<sup>1</sup>. Sometimes health professionals use inadequate analgesics in fear of its adverse effects like nausea, vomiting, respiratory depression etc. Moreover, many drugs are too costly. But it is patients' right to get adequate relief of pain in post operative period.

Ketorolac and Nalbuphine are two widely used drugs in management of acute pain. Nalbuphine is a synthetic opioid analgesic with both narcotic agonist and antagonist action. It acts as a strong kappa receptor agonist and is a mu receptor

antagonist when given parenterally<sup>2</sup>. Its analgesic potency and efficacy is almost equal to morphine and meperidine<sup>3,4</sup>. It is shown in the study that it is safe, even in pre-hospital management of pain in burn, multiple trauma, orthopedic injury and intra abdominal conditions<sup>5</sup>. Another study also shows that Nalbuphine is proved as a useful substitute for meperidine in orthopedic surgery<sup>6</sup>.

Ketorolac is an NSAID with intermediate duration of action (Half life: 4-6 hrs). It is used mainly as analgesic. Ketorolac can be used to replace morphine successfully for mild to moderate post surgical pain. Like other Non Steroidal Anti-inflammatory Drug (NSAID) it has analgesic, antipyretic and anti-inflammatory action<sup>7</sup>. This is usually indicated for short term management of acute post operative pain. In contrast Morphine and meperidine requires close and costly monitoring because of respiratory depression and shock.

Costly health care system is not feasible for the people of Bangladesh. This is also true in case of post operative pain management. So it is important to find a safe and effective analgesic with minimum cost for post operative patients. Ketorolac and Nalbuphine are used to manage acute post operative pain. Both of them are less costly than strong opioids available in the local market. So it is the point of interest whether these drugs are similarly effective in post operative pain management in orthosurgical procedures. Aim of this study was to identify the effective analgesic for post-operative period in orthopedic surgery by comparing to commonly used analgesic-injectable Ketorolac and Nalbuphine.

## MATERIALS AND METHODS

The study was designed as double blind randomized clinical trial and was conducted in the Department of Orthopedics. Sylhet M A G Osmani Medical College Hospital, Sylhet in the year of 2009 (From January to December). Patients with age more than 18 years were included. Exclusion criteria were Physical status ASA 2 to 5, Patient with cardiac, renal, hepatic, endocrine, or immunologic disease, patients who were known to be allergic to any drugs under study, Patients with active psychiatric disorder, mental retardation or complications that were too severe to allow normal communication. Subjects were randomized by Simple random sampling using 'Random Number Table'. The samples were again divided into 2 groups by Lottery method. These were: Group-A : The patients in this group received Intravenous Ketorolac ( 30 mg ) 6 hourly as intravenous doses for 48 hours post operatively. Group-B : The patients in this group received Intravenous Nalbuphine (20 mg) 6 hourly as intravenous doses for 48 hrs postoperatively.

The patients were counseled regarding the procedures of the study and methods of pain assessment by Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS). Informed written consent was obtained from each patient included in the study. The operations were done by the senior surgeons in the Department of Orthopedics in Sylhet MAG Osmani Medical College Hospital, Sylhet to minimize the tissue injury and to maintain the optimum quality of surgery. Both drugs were applied via intravenous route just after operation and this point was regarded as '0' hour. Drugs were continued as 6 hourly I.V doses by trained nurses and the patients were followed up at 1, 6, 12, 24, 32 and 48 hours. At each time patients were asked to mark their current assessment of pain on both Visual Analog Scale (VAS) and Numeric Rating Scale (NRS). At the same time pulse, blood pressure, respiratory rate, and sedation score were recorded. Each time patient was asked for any unwanted effects. The data were recorded in a pre-designed data collection form. Data were analyzed statistically using Microsoft Excel and significance of the data were test with Chi-square test and Z-test.

## RESULTS

In this study included 68 samples in each groups in the defined time period. But 3 respondents in group A and 1 respondent in group B refused to participate in this study later on. So finally this study included 132 respondents of which 65 (49.24%) were treated with inj. Ketorolac (30mg) (Group-A) and 67 (50.76%) were treated with inj. Nalbuphine (20mg) (Group-B). Among Group – A 72.31% were male and 27.69% were female. While in Group -B 64.18% were male and 35.82% were female. Mean age of Group-A and Group-B were  $40.28 \pm 13.03$  and  $40.74 \pm 16.84$  respectively. The mean age of total respondents in this series was  $40.52 \pm 15.03$ . This age and sex distribution of this study proved statistically homogenous. ( $\chi^2 = 1.004$ ,  $df = 1$ ,  $p > 0.05$ ). Operation done during this study was mentioned in Table -I. At 1<sup>st</sup> hour the VAS score of group B was higher by 0.06 but the difference was not significant statistically with Z – test ( $Z = 0.6$ ,  $p > 0.05$ ). From 6<sup>th</sup> hour onward the VAS scores of Group B were less than the scores of Group A and differences were highly significant statistically ( $p < 0.01$ ) (Table II).

At 1<sup>st</sup> hour the NRS scores of both groups did not show any significant difference though the score of Group B was a bit high by 0.15 ( $Z = 0.63$ ,  $p > 0.05$ ). but from 6<sup>th</sup> hour the NRS scores of Group B were less than the scores of Group A and the differences were significant statistically ( $p < 0.05$ ). This trend of response was maintained in the subsequent follow-up till 48 hours. At 32 and 48 hours the differences of NRS

scores of group B were highly significant with Z-test ( $p < 0.01$ ). (Figure 1). Difference of decrement of pulse rate in Nalbuphine treated group was statistically significant from the 6<sup>th</sup> hour to subsequent follow-up upto 48<sup>th</sup> hour. ( $p < 0.05$  or  $0.01$ ) (Figure 2).

The whole follow-up period the respiratory rate of group B were significantly less with Z-test. ( $p < 0.05$  or  $0.01$ ) (Figure 3). Systolic pressures of the respondents were declined gradually in the rest of the follow-up period after 6 hours and the decrement was significantly marked in group B ( $p < 0.001$ ) (Figure 4). Difference of mean diastolic pressure in this series proved insignificant with Z-test ( $p > 0.05$ ) throughout the whole follow-up period.

The post analgesic sedation score was significantly lower in group B than group A from 6 hour onward. ( $Z = 2.2$ ,  $p < 0.05$ ) and the difference of mean value of sedation score between group A and group B became highly significant from 24 hour to end of the follow-up period ( $p < 0.01$  or  $p < 0.001$ ). At 12 hour the difference of sedation score was insignificant ( $p > 0.05$ ) (Table III). The main adverse effect observed in the group-A was heart burn and nausea or nausea & vomiting whereas in group-B main adverse effect was nausea. No event of respiratory depression or shock was found in this series (Figure 5).

**Table I :** Types of operations done.

Name of operations	Treatment group		Total
	Group A	Group B	
Closed reduction and internal fixation by DHS	8	5	13
Closed reduction and internal fixation by DCS	3	2	5
Closed reduction and internal fixation by Hip screw	2	1	3
ORIF by Small DCP	7	8	15
ORIF by Broad DCP	1	2	3
ORIF by Narrow DCP	5	7	12
ORIF by Rush nail	7	4	11
ORIF by K- nail	10	14	24
Above knee amputation	3	4	7
Bellow knee amputation	1	2	3
Hemiarthroplasty ( Hip joint)	4	3	7
Tendon transfer	1	2	3
Skin grafting	6	7	13
Sequestrectomy & Saucerisation	2	1	3
ORIF of Pubic symphysis diastasis.	0	1	1
Curettage & Bone graft for GCT	2	2	4
Biopsy from bone tumor	3	2	5
Total	65	67	132

Group A: Ketorolac treated, Group B: Nalbuphine treated, ORIF: Open Reduction & Internal Fixation, DCP: Dynamic Compression Plate, GCT: Giant Cell Tumor.

**Table II :** Assessment of Post operative Pain by VAS.

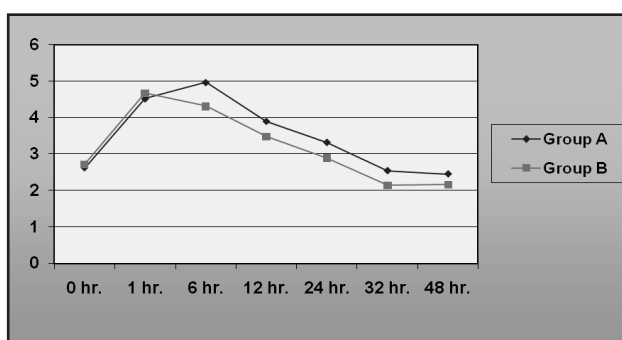
Time period	Group A	Group B	Z Test for Group A & B (df 130)	
	VAS score (cm) (Mean $\pm$ SD)	VAS score (cm) (Mean $\pm$ SD)	Z value	p value
At 0 hr.	2.60 $\pm$ 1.06	2.72 $\pm$ 1.23	0.60	> 0.05
After 1 hr.	4.49 $\pm$ 1.30	4.55 $\pm$ 1.48	0.25	> 0.05
After 6 hr.	4.97 $\pm$ 1.13	4.30 $\pm$ 1.29	3.18	< 0.01
After 12 hr.	3.95 $\pm$ 1.03	3.44 $\pm$ 0.96	3.00	< 0.01
After 24 hr.	3.34 $\pm$ 1.17	3.05 $\pm$ 0.75	9.67	< 0.001
After 32 hr.	2.54 $\pm$ 0.79	2.10 $\pm$ 0.58	3.14	< 0.01
After 48 hr.	2.45 $\pm$ 0.64	2.19 $\pm$ 0.47	2.65	< 0.01

Group A : Ketorolac treated, Group B : Nalbuphine treated.

**Table III :** Assessment of sedative effect by 'Sedation score.

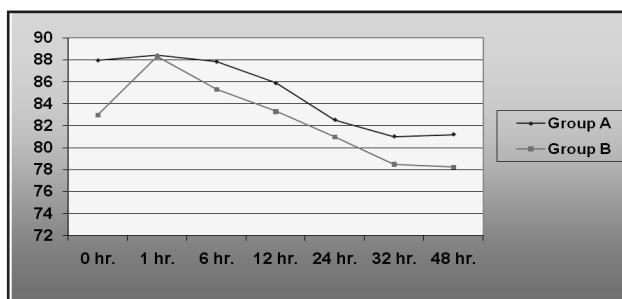
Time period	Group A	Group B	Z value	df	p value
	Sedation score (Mean $\pm$ SD)	Sedation score (Mean $\pm$ SD)			
At 0 hr.	3.26 $\pm$ 0.69	3.28 $\pm$ 0.87	0.15	130	> 0.05
After 1 hr.	3.6 $\pm$ 0.49	3.73 $\pm$ 0.45	1.60	130	> 0.05
After 6 hr.	3.66 $\pm$ 0.48	3.45 $\pm$ 0.61	2.20	130	< 0.05
After 12 hr.	3.26 $\pm$ 0.80	3.07 $\pm$ 0.47	1.66	130	> 0.05
After 24 hr.	3.17 $\pm$ 0.38	2.87 $\pm$ 0.70	3.07	130	< 0.01
After 32 hr.	2.65 $\pm$ 0.48	2.27 $\pm$ 0.75	3.48	130	< 0.001
After 48 hr.	2.71 $\pm$ 0.46	2.27 $\pm$ 0.64	4.55	130	< 0.001

Group A : Ketorolac treated, Group B : Nalbuphine treated.



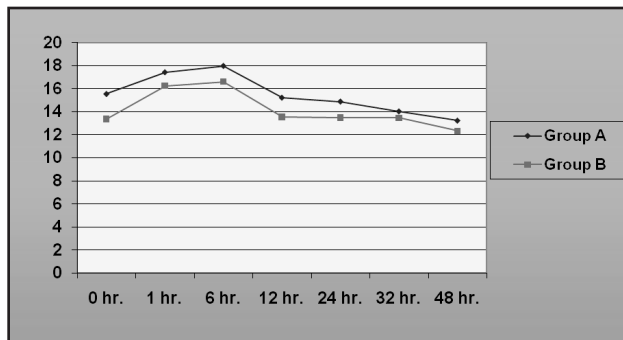
**Figure 1:** NRS scores of respondents.

Group A : Ketorolac treated, Group B : Nalbuphine treated.

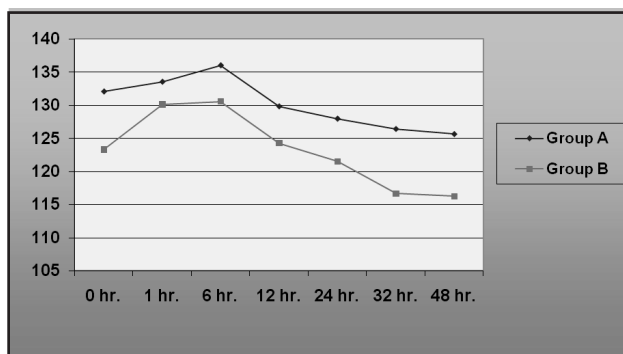


**Figure 2 :** Linear illustration of pulse rate of respondents.

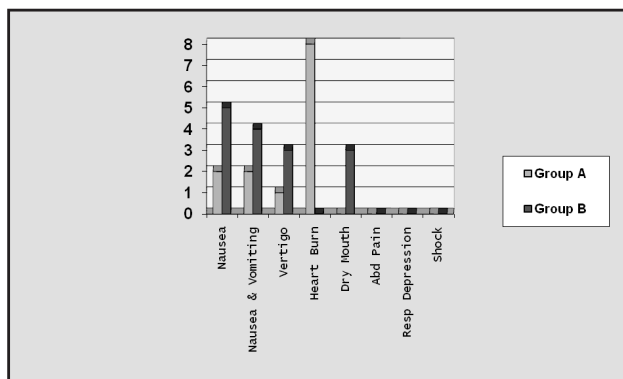
Group A : Ketorolac treated, Group B : Nalbuphine treated.



**Figure 3 :** Mean Changes of respiratory rate of respondents. Group A : Ketorolac treated, Group B : Nalbuphine treated.



**Figure 4 :** Changes of systolic pressure. Group A: Ketorolac treated, Group B : Nalbuphine treated.



**Figure 5 :** Adverse effects in the respondents. Group A: Ketorolac treated, Group B : Nalbuphine treated.

## DISCUSSION

An effective analgesic is desired in post operative period of orthopedic surgery that should have adequate sedative effect and devoid of any serious complications and cost effective as well.

It was found that both Ketorolac and Nalbuphine decrease the pain level below the VAS score 4 within 12 hours and it was persistently maintained in the both treatment groups<sup>8</sup>. VAS scores were decreased further more gradually. This indicates, both Ketorolac and Nalbuphine are potent analgesics in case of orthopedics surgery. Regarding post

operative pain management this type of efficacy of Nalbuphine and ketorolac were supported by some previous studies<sup>8,9</sup>. Johansson S et al also showed that intravenous Ketorolac was effective and safe in the management of moderate to severe post operative pain in the orthopedic surgery<sup>10</sup>. Drasner commented in his study that Ketorolac had provided physicians with a non-opioid alternative for the treatment of mild to moderate post operative pain and a useful adjunct to decrease the opiate requirement of moderate to severe pain<sup>11</sup>.

It was found that the VAS scores of the Nalbuphine treated group were significantly lower than the Ketorolac treated group from 12 hour onwards that indicated the better compliance of Nalbuphine in the treatment of post operative pain. A study also found that the analgesia with intravenous Ketorolac developed more slowly than intravenous Nalbuphine and sum of the pain intensity difference numerically favoured nalbuphine<sup>3,6</sup>. Schmidt W. K also admitted the efficacy of Nalbuphine over NSAIDs in the management of postoperative pain<sup>12</sup>. A recent study concluded that Nalbuphine produce clinically significant analgesia and sedation when compared to Tramadol and Ketorolac<sup>13</sup>. Another study revealed that Intravenous Ketorolac was found significantly more effective than intravenous Nalbuphine in children at post operative period in case of adenotonsillectomy<sup>14</sup>.

Though not so high but there was an initial rise of VAS score in 1<sup>st</sup> hour in both treatment groups. This might be due to gradual recovery from anaesthesia after operation as most of the procedures were performed under regional block like spinal anaesthesia, supraclavicular block or nerve block. Here also VAS score did not cross the moderate level (4-7). Pain assessment through NRS also showed similar type of response.

Patient's pulse rate and systolic blood pressure rises have a strong association with the perception of pain. So at 1<sup>st</sup> hour rise in pulse rate and systolic blood pressure may be due to perception of pain following the recovery of the effect of regional anaesthesia. Then pulse rate declined gradually at both group but more evident in Nalbuphine treated group which was highly significant ( $p < 0.01$ ). This indicated the better efficacy of Nalbuphine than Ketorolac. But neither Ketorolac nor Nalbuphine produced bradycardia in any of the subject. The study of Miller R. R showed that Inj. Nalbuphine had very few effects on cardiovascular haemodynamics in a patient without prior cardiovascular disease<sup>2</sup>. There was mild rise of systolic blood pressure in both groups in first 6 hours but less with Nalbuphine treated group. Rise of mean blood pressure remains within 20% of base line with Nalbuphine in the peri-operative period<sup>15</sup>. After wards systolic blood

pressure declined gradually with the effect of analgesics in both groups. Throughout the whole follow up period the decrement of systolic blood pressure in the Nalbuphine treated group was significantly lower ( $p < 0.05$ ). Here diastolic blood pressure varied a little bit which was statistically proved insignificant ( $p > 0.05$ ). No significant cardiovascular adverse effect was found in several published studies<sup>3,5,12,16</sup>.

This study shows the rise of respiratory rate in 1<sup>st</sup> 6 hours but it did not show tachypnoea. During subsequent follow up respiratory rate declined gradually in both groups. This decrement was more in Nalbuphine treated group. But no event of respiratory depression was observed. The study of Lefevre B and Schmid W. K. (1985) drew the similar inference that Nalbuphine produced no respiratory depression at post operative period<sup>17,12</sup>. No unwanted effects on respiratory rate was found with inj. Ketorolac in the study of Stene J. K. et al<sup>18</sup>.

State of sedation is an important association with the state of analgesia. Increased sedation score indicates the less sedative effect of a drug. No significant difference in sedation scores were found in first 6 hours between 2 groups. From the 6<sup>th</sup> hour and onwards sedation scores of Nalbuphine treated group was significantly lower. This was probably due to depressive pharmacological effect of Nalbuphine on CNS as it is a weak opioid. Such sedative effect of Nalbuphine was also proved in the study of Mitterschiffthaler G. and Huter O<sup>19</sup>.

Serious adverse effects like shock, respiratory depression abdominal cramp were not observed in this series in any group. Very few adverse effects were observed like nausea and vomiting or mild vertigo which were managed with medication. So both drugs used in this study were safe at post operative pain management.

Some published data even concluded that Injectable Nalbuphine could be an alternative to Inj. Pathedine or morphine at Post operative pain management.<sup>2,4,12,20</sup>.

## CONCLUSION

This study concluded that both Ketorolac and Nalbuphine can be used safely and effectively through intravenous route at 6 hourly doses to manage post operative pain in Orthopedic surgery for the 1<sup>st</sup> 48 hours. Moreover among this two drugs inj. Nalbuphine is superior. Therefore either of these two drugs, especially Nalbuphine, may be an alternative to strong opioid for the management of post operative pain in orthopedics surgery. A multi-center double blind randomized clinical trial could be designed with large sample size to justify the result of this study.

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## DISCLOSURE

All the authors declared no competing interest.

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