



Comparison on the Effects Of Butorphanol And Nalbuphine During Balanced Anaesthesia For Upper Abdominal Surgery- A Randomized Clinical Trial

Dr. Mohammad Kamaluddin Vahrott¹, Dr. Yumnam Arun Kumar Singh², Dr. Pradipkumar Singh³,
Dr. Noorjahan¹, Dr. Sonia Naorem¹, Dr. Pabin Pious¹

¹PGT, ²Assistant Professor, ³Professor

Department of Anaesthesiology, Regional Institute of Medical Sciences, Lamphelpat, Imphal West, Manipur,
India. PIN- 795004

***Corresponding Author:**

Dr. Yumnam Arun Kumar Singh

Department of Anaesthesiology, Regional Institute of Medical Sciences, Lamphelpat, Imphal West, Manipur,
India. PIN- 795004

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Abstract

Background:

Narcotics such as nalbuphine and butorphanol have been emerging as an effective analgesics apart from its antianxiety and hypnotic property. Thus, in search for the ideal drug we compare the role of nalbuphine and butorphanol for balanced anaesthesia with decreased post-operative complications such as prolonged awakening, respiratory depression, nausea, vomiting and high addiction potential.

Materials and methods:

The study was a randomized, controlled trial in which 80 adult patients aged 18-60 years, of both sex, ASA I&II, undergoing upper abdominal surgery under general anaesthesia were randomly assigned into two groups of 40 patients each to receive inj nalbuphine 0.1mg/kg and inj butorphanol 20µg/kg 5 minutes prior to intubation during balanced anaesthesia adjusting the anesthetic depth to Bispectral index (EEG guided anaesthetic depth monitoring) of 40 to 60. The emergence time, extubation time, time to reach Ramsay sedation score of 2, duration of analgesia, haemodynamic parameters, sedation, postoperative nausea and vomiting (PONV) and intraoperative dreams in the recovery room were recorded and compared.

Results:

The emergence time, extubation time, time to reach Ramsay sedation score of 2, duration of anaesthesia and haemodynamic parameters were comparable in the two groups ($P>0.05$). The duration of analgesia was longer in nalbuphine group with minimal intraoperative dreams and side effects such as PONV and shivering.

Conclusion:

Nalbuphine had better recovery profile compared to butorphanol along with longer duration of analgesic potency with lesser side effects under the BIS guided balanced anaesthesia.

Keywords: Nalbuphine, Butorphanol, recovery profile, bispectral index

Introduction

The use of intravenous narcotics in balanced anaesthesia is a well-recognized technique in anaesthesia. Preoperative narcotic analgesics not only allay patients' apprehension but also reduce the dose of intravenous and inhalation agents necessary to

achieve surgical anaesthesia. Furthermore, they reduce the need for analgesics in the early postoperative period. Disadvantages of these drugs include prolonged awakening, nausea and/or vomiting, respiratory depression, and a high addiction potential.^[1]

A drug which would retain the benefits of existing narcotics but eliminates their disadvantages would be advantageous.^[2] Nalbuphine and Butorphanol are agonist-antagonist opioid analgesics with cardiovascular stability and lesser potential for respiratory depression.^[3] Butorphanol 2mg and Nalbuphine 10mg are considered equianalgesic to morphine 10mg.^[4] Some earlier study has already compared butorphanol 2mg and nalbuphine 10mg during neurosurgery, keeping haemodynamic parameters within 20% of the baseline. In our set-up with relatively short duration of operation, we would like to compare butorphanol 20µg/kg (approx. 1mg) with nalbuphine 0.1mg/kg (approx. 5mg) during balanced anaesthesia adjusting the anesthetic depth to Bispectral index (EEG guided anaesthetic depth monitoring) of 40 to 60 instead of haemodynamic parameters which can vary the magnitude of blood loss or surgical stress.^[5]

Materials And Methods

The study was a randomized, controlled, double-blinded one conducted at a tertiary care centre, Imphal, Manipur during two years period starting from September 2018 to October 2020. With due approval from Institutional Ethical Committee and Clinical Trial Registry of India, written informed consent were taken from patient of only indigenous population of Manipur, of American Society of Anaesthesiologists (ASA) physical status I or II, of both sex, aged 18- 60 years scheduled to undergo elective upper abdominal surgeries. Patients with hepatic, renal, neurological disorders and neuropathies, known allergy to a particular drug, compromised cardiovascular and respiratory problems and anticipated difficult airway were excluded from the study.

Sample size was calculated based on a previous study by Dulara SC *et al* ^[5] for alpha value of 5% and power of 80% assuming a difference of 15% in the mean duration of recovery of consciousness. So, 80 patients were assigned into two groups of 40 each based on computer generated randomization viz: Group N: patients received nalbuphine 0.1mg/kg 5 minutes before induction of anaesthesia and Group B: patients received butorphanol 20µg/kg 5 minutes before induction of anaesthesia. The primary investigator and the patient were blinded of the group

allotment and the study drugs were prepared by an anaesthetist not involved in the study.

Preoperative assessment was done a day prior to the scheduled day of surgery. All patients received Tab Alprazolam 0.25 mg the night before the surgery. Inj. metoclopramide and inj. ranitidine 50 mg were given intravenously in the morning of surgery in the pre anaesthetic room and intravenous assess was established to start the maintenance fluids. On arrival to the operation theatre baseline monitoring of pulse rate (PR), non-invasive blood pressure (NIBP) and oxygen saturation (SpO₂) and electrocardiogram (ECG) were started. Care was taken to maintain normothermia in the operation theatre.

According to the group assigned, injection butorphanol 20µg/kg or injection nalbuphine 0.1mg/kg was given slow I.V (intravenous) 5 minutes before (2 minutes before preoxygenation with 100% O₂ for 3 minutes) induction of anaesthesia with propofol 1.5mg-2mg/kg followed by injection rocuronium 0.9mg/kg to facilitate endo-tracheal intubation. Just after endotracheal intubation anaesthesia was maintained with a combination of 50% Nitrous oxide in oxygen with traces of sevoflurane 0.6 to 2% to keep the BIS value between 40-60. Total fresh gas was kept at 2 L/min (50% N₂O and 50% O₂) and ventilation was adjusted to keep the end tidal carbon dioxide tension (ETCO₂) between 30-35mm Hg.

As we planned to include the assessment of stress response to laryngoscopy and endotracheal intubation, intra-operative haemodynamic parameters (heart rate, systolic/diastolic/mean arterial pressure) were recorded at 3 minutes after giving the study drug, then just after laryngoscopy and endotracheal intubation followed by recording every minute for 5 minutes and again at 10 minutes of intubation. Thereafter recordings were made at 5 minutes interval for the first hour and every 10 minutes for the second hour till the end of the surgery. Residual neuromuscular blockade was reversed with injection neostigmine 0.05mg/kg and injection glycopyrrolate 0.008mg/kg. Sevoflurane vapourizer was closed approximately 10 minutes before the anticipated end of skin closure. Nitrous oxide was stopped 2 minutes before giving neuromuscular block reversal. Emergence time was taken as the time from the stoppage of inhalational agents to eye opening on

command. At this point the endotracheal tube was removed when patient breathed spontaneously with adequate tidal excursion. The later was to be noted as extubation time. After shifting to the post anaesthesia care unit (PACU) patient's level of sedation was assessed by Ramsay Sedation Scale [6] It was checked every 15 minutes and time to reach Ramsay scale 2 was noted. Duration of analgesia was taken as time from the injection of the study drug till the patient complains of pain (Visual Analogue Scale [7] >4) seeking the first rescue analgesia. Rescue analgesic was given with inj. Diclofenac (aqueous) 75mg IM or slow IV. Other complications such as post-operative nausea and vomiting (PONV), chills, respiratory depression, etc were recorded.

All the datas collected were tabulated in excel format and analysed using SPSS software of 21st version. Chi-square test was used to find out the association between proportion, T-test test was used to see the association between mean of groups appropriately. A p-value less than 0.05 was considered significant. Steps were taken up to maintain confidentiality and datas collected were kept under lock and key.

Results And Observations

The study protocol was completed in all the enrolled 80 patients. The demographic parameter such as age, ASA, height and weight were comparable in all the three groups and did not affect the study outcome, as shown in table 1.

Table 1 : Demographic Profile of the three study groups (N=80)

Parameters	Group N (N=40)	Group B (N=40)	P value
Age years, mean (±SD)	44.95±13.87	41.83±13.39	P = 0.31
ASA Grading (I:II)	37:8	39:6	P = 0.79
Gender (M/F)	12:28	11:29	P = 0.16
Weight mean (kgs) (±SD)	53.95±8.90	54.90±9.66	P = 0.64

P<0.05 is significant

Table 2. Comparison and distribution of duration of anaesthesia, extubation Time, recovery of consciousness, duration of analgesia, intraoperative dreams and PONV in the two groups.

Parameters	Group N (N=40)	Group B (N=40)	P = Value
Duration of Anaesthesia mean (±SD)	70.25±13.98	71.70±17.85	
Extubation Time mean (±SD)	10.73±3.162	11.48±3.38	0.30
Recovery of Consciousness mean (±SD)	9.68±3.38	10.68±3.73	0.61

<i>Duration of Analgesia mean (±SD)</i>	109.45±14.89	99.08±24.82	0.02
<i>Intraoperative Dreams</i>	1(2.5%)	5(2.5%)	0.09
<i>Post Operative nausea and Vomitting</i>	0	1(2.5%)	0.32

P<0.05 is significant

The duration of anaesthesia, extubation time, recovery of consciousness, and PONV were comparable in the two groups (not significant) even though lower values were recorded in the nalbuphine group, as shown in Table 2. However, significant longer duration of analgesia and lesser intraoperative dreams were also observed in the nalbuphine group.

Table no. 3. Comparison and distribution of mean changes from baseline of Bi Spectral Index in two groups

BIS	Group N <i>mean (±SD)</i>	Group B <i>mean (±SD)</i>	P value
Baseline	95.08±1.18	95.05±1.69	0.68
At 1 min	-45.25±4.41	-43.25±7.47	0.14
At 2 mins	-44.70±4.05	-39.37±7.32	0.00
At 3 mins	-43.07±4.28	-39.07±5.64	0.00
At 4 mins	-42.85±3.23	-37.40±6.07	0.00
At 5 mins	-42.50±3.43	-35.70±7.98	0.00
At 10 mins	-42.90±3.71	-39.05±8.28	0.00
At 15 mins	-41.82±5.43	-38.82±10.55	0.11
At 30 mins	-42.82±3.84	-37.47±12.85	0.14
At 45 mins	-42.50±3.51	-36.60±14.02	0.01
At 60 mins	-41.58±4.87	-36.02±12.78	0.01
At 75 mins	-37.29±7.59	-37.40±9.07	0.96
At 90 mins	-32.88±12.71	-28.50±20.92	0.64
At 120 mins	-45.00±0.00	-46.00±7.07	0.86

P<0.05 is significant

The BIS value immediately after intubation between the 2 groups were statistically significant (P value < 0.05) at 2nd minutes, 3rd minutes, 4th minutes, 5th minutes, 10th minutes, 30 minutes, 45 minutes and 60th minutes with lower values recorded in the nalbuphine group, as shown in table 3. At all other times intra-operatively up to 120 minutes, BIS value was not statistically significant (P value > 0.05).

Table 4 . Comparison of changes in the mean heart rate from the base line in the two groups

Heart Rate (bpm)	Group N <i>mean (±SD)</i>	Group B <i>mean (±SD)</i>	P value
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Baseline	82.55±9.94	82.73±12.25	.94
At 1 min	17.00±6.53	11.08±11.73	0.00
At 2 mins	14.50±5.51	7.93±14.29	0.00
At 3 mins	11.40±7.58	5.22±13.93	0.01
At 5 mins	7.27±7.42	1.37±13.76	0.01
At 10th mins	6.70±7.70	0.17±13.07	0.00
At 15th mins	3.90±6.98	-1.45±16.56	0.06
At 30th mins	0.20±7.20	-2.42±12.05	0.24
At 45th mins	2.17±6.60	-4.15±12.63	0.38
At 60th mins	1.20±7.49	-2.88±15.72	0.54
At 75th mins	1.21±6.37	-2.00±15.23	0.32
At 90th mins	1.11±9.53	-8.75±6.18	0.08
At 120th mins	1.50±6.36	13.00±14.14	0.40

P<0.05 is significant

The comparison of hemodynamic parameter, shown in table 4 and 5, such as heart rate (HR) and MAP among the two groups were comparable and statistically not significant (P value of 0.94). However significant increased value of heart rate were noted at 1st, 2nd, 3rd, 5th, 10th minutes post intubation in the nalbuphine group.

Table no.5 comparison of mean changes from the baseline value of arterial blood pressure (mm Hg) in both groups

MAP (mm Hg)	Group N <i>mean (±SD)</i>	Group B <i>mean (±SD)</i>	P value
Baseline	82.70±7.68	86.43±10.42	.073
At 1 mins	17.27±8.72	13.00±19.32	0.20
At 2 mins	12.60±9.28	9.45±18.73	0.34
At 3 mins	9.30±11.01	3.22±14.77	0.04
At 5 mins	7.27±7.42	1.37±13.76	0.01
At 10 mins	3.20±11.54	3.82±9.94	0.76
At 15 mins	3.90±6.98	-1.45±16.56	0.06
At 30 mins	0.20±7.20	-2.42±12.05	0.24
At 45 mins	-0.52±7.40	3.72±123.68	0.22
At 60 mins	1.22±8.60	4.60±12.39	0.77
At 75 mins	1.21±6.37	-2.00±15.23	0.67
At 90 mins	1.55±7.79	3.80±13.71	0.69
At 120 mins	-1.50±6.36	-1.00±14.14	0.40

P<0.05 is significant

The comparison of hemodynamic parameter, shown in table 4 and 5, such as heart rate (HR) and MAP among the two groups were comparable and statistically not significant (P value of 0.94). However significant increased value of heart rate were noted at 1st, 2nd, 3rd, 5th, 10th minutes post intubation in the nalbuphine group.

Discussion:

There is a strong demand for faster anaesthesia recovery, as a quicker recovery may be associated with earlier and better care of patent airways, more protection against aspiration, and greater oxygenation. From an economic perspective, a quick anaesthesia recovery favours fast-tracking, increases case turnover and may improve resource use^[8]. In a previous study, Epstein et al^[9] concluded that prolonged extubation time should be treated as resulting in proportionally increased variable cost.

Surgery and anaesthesia induce considerable emotional stress in patients. Age, previous hospital experiences and type of surgery are the factors that can influence a patient's anxiety level and psychological wellbeing in the recovery phase. There are multiple goals of pharmacologic premedication; of these one of the goals is to provide preoperative sedation with anxiolysis and analgesic to maintain a balance between patient's comfort and safety. Narcotic analgesics are used preoperatively because they alleviate apprehension and reduce the dose of intravenous and inhalation agents necessary to achieve surgical anaesthesia. Furthermore, they reduce the need for analgesics in the early postoperative period. Pallasch TJ et al^[10] found that both the agonist/antagonist analgesics butorphanol and nalbuphine are equianalgesic and nalbuphine is equipotent with morphine.

The Bispectral Index, a quantitative parameter derived from the frontal electroencephalogram has been validated as a measure of cerebral drug effect in subjects older than 1 year^[11]. BIS value between 40 and 60 reflects adequate hypnotic effect of general anaesthesia with reasonably rapid recovery of consciousness.^[12] Our study recorded significant difference in BIS value after induction of general anaesthesia followed by laryngoscopy and intubation at 2nd, 3rd, 4th and 5th minutes in the two groups but the BIS values were in the clinically accepted range of 40-60 which was a reflection of the fact that both

the groups received the same drugs for intravenous induction. These findings were similar to a previous study by Nakayama et al.^[13]

The duration of anaesthesia, extubation time and recovery of consciousness were comparable ($P > 0.05$) in the two groups even though lesser value were recorded in the nalbuphine group. Similar findings were also reported by independent studies of Nikoda VV et al^[14] and Dulara SC et al.^[5] The mean Ramsay sedation score 2 was achieved at 19.88 ± 7.88 and 20.25 ± 8.00 minutes after extubation in group N and B respectively which is comparable ($P < 0.83$). This shows that sedation is an unavoidable side effect of both Butorphanol and Nalbuphine when given in adequate doses but it is more with Butorphanol than Nalbuphine in this study. Verma RK et al^[3] and Sofia D et al^[15] also recorded similar results in their study.

There was no significant difference regarding hemodynamic parameters in the two groups throughout the study period except in the early period post intubation group N showed highest significant increase in heart rate. Similar results were recorded by Mishra LD et al^[16] and Del Pizzo A et al^[17].

The mean duration of first rescue analgesic in the group N was 109.45 ± 14.89 while in the group B, it was 99.08 ± 24.82 which shows that Nalbuphine group has significant longer duration compared to Butorphanol. Mishra LD et al^[16] conducted a study in sixty patients undergoing craniotomy to assess the analgesic effects of butorphanol and found to be safe intraoperative analgesic in neurosurgical patients. Minai FN et al^[18] compared morphine and nalbuphine for intraoperative analgesia. They concluded that nalbuphine in a dose of 0.2mg/kg provided better analgesia and greater haemodynamic stability, as a component of balanced anaesthesia.

The incidence of side effects such as PONV were almost absent in the two groups and this findings were reported by Fragen RJ et al^[2] who opined that patients receiving nalbuphine experienced less nausea and/or vomiting post-operative than those in the other. Group N had lower insignificant incidence of intraoperative dreams recall than B group and our study correlates with the results of Leslie K et al^[19] Dreaming during anaesthesia is unrelated to the depth of anaesthesia in almost all cases. Similarities with dreams of sleep suggest that anaesthetic dreaming occurs during recovery, when patients are sedated or

in a physiologic sleep state. The incidence of chills and shivering was nil in our study and co-relates well with the study findings of Vogelsang et al^[20].

Conclusion

Nalbuphine had better recovery profile in regards to emergence time, extubation time, Ramsay Sedation Scale under BIS guided balanced anaesthesia even though the results are not statistically significant. The intraoperative haemodynamically stability was equipotent in both the study groups although marked increased heart rate were observed with nalbuphine in early periods of laryngoscopy and post intubation. Nalbuphine had longer duration of analgesic potency. There was less incidence of post-operative nausea and vomiting and other side effects in the nalbuphine group.

We found that nalbuphine had the best recovery profile compared to butorphanol along with better and longer duration of analgesic potency including lesser side effects under the BIS guided balanced anaesthesia.

References

1. Dobkin AB, Arandia HY, Byles PH, Africa BF, Carusa FS. Butorphanol tartrate: safely and efficacy in balanced anaesthesia. *Can Anaesthesia Soc J* 1976;23:601-8.
2. Fragen RJ, Caldwell N. Acute premedication with nalbuphine. *Anaesth Analg* 1977; 56:808-12.
3. Verma RK, Jaiswal S, Rao-PB-Singh. IV Total Intravenous Anaesthesia In Laparoscopic cholecystectomy: Comparison of Butorphanol and Fentanyl. *The Internet J Anaesth* 2007; vol 14. (1):1-7.
4. McCammon RL, Stoelting RK, Madura JA. Effects of Butorphanol, Nalbuphine, and Fentanyl on Intrahepatic Tract Dynamics. *Anaesth Analg* 1984; 63:139-42.
5. Dulara SC, Chhabra S.A comparative study of butorphanol and nalbuphine using propofol and isoflurane in patients undergoing craniotomy under general anaesthesia. *National Monthly Ref J Res in Sci Tech* 2010;2(7);40-50.
6. Ramsay MAE, Savege TM, Simpson BRJ and Goodwin R. Controlled sedation with alpraxalone- alphadolone. *British Medical Journal* 1974; 2:656-9.
7. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? *Pain*. 1997 Aug;72(1-2):95-7.
8. Jakobsson J. Desflurane: a clinical update of a third-generation inhaled anaesthetic. *Acta Anaesthesiol Scand*. 2012 Apr;56(4):420-32.
9. Epstein RH, Dexter F, Brull SJ. Cohort study of cases with prolonged tracheal extubation times to examine the relationship with duration of workday. *Can J Anaesth*. 2013 Nov;60(11):1070-6.
10. Pallasch TJ, Gill CJ. Butorphanol and Nalbuphine: A pharmacologic comparison. *Oral surgery, Oral medicine, Oral pathology* 1985;59(1):15-20.
11. Schwartz D, Wu A, Han D, Gibson C, Connelly NR. BIS in children during maintenance anaesthesia. *Rom J Anaesth Intensive Care* 2011;18(2):95-100.
12. Brown E, Solt K, Purdon P, Johnson-Akeju O. Monitoring brain state during general anaesthesia and sedation. In: Miller RD, editor. *Miller's Anaesthesia* 8th ed. Philadelphia: Elsevier Churchill Livingstone; 2015. p. 1526–30.
13. Nakayama M, Ichinose H, Namiki A. The effect of fentanyl on haemodynamic and Bispectral index changes during anaesthesia induction with propofol. *J Clin Anesth* 2002 Mar;14(2):146-9.
14. Nikoda VV et al. The evaluation of the efficacy and safety of using nalbuphine hydrochloride (Nubain) in patients in the early postoperative period. *Anesteziol Reanimatol* 1994 Mar-Apr;(2):40-3.
15. Sofia D et al. Effects of Fentanyl And Butorphanol on Induction Dose of Propofol in Adults. *IOSR Journal of Dental and Medical Sciences* 2017 May;16(4):48-53.
16. Mishra LD, Rajkumari N, Singh SN, Dubey RK, Yadav G. A comparative study of Propofol and Isoflurane Anaesthesia using Butorphanol in Neurosurgery. *Indian J Anaesth* 2009;53(3):324-9.

17. Del Pizzo A. A double-blind study on the effects of butorphanol compared with morphine in balanced anaesthesia. *Can Anaesth Soc J* 1978 Sep;25(5):392-7.
18. Minai FN, Khan FA. A comparison of morphine and nalbuphine for intraoperative and postoperative analgesia. *J Pak Med Assoc.* 2003;53(9)391-5.
19. Leslie K, Skrzypek H, Paech MJ, Kurowski I, Whybrow T. Dreaming during anesthesia and anesthetic depth in elective surgery patients: a prospective cohort study. *Anesthesiology* 2007 Jan;106(1):33-42.
20. Vogelsang J, Hayes SR. Butorphanol tartrate (Stadol) relieves post anesthesia shaking more effectively than meperidine (Demerol) or morphine. *J Post Anesth Nurs.* 1992 Apr;7(2):94-100.