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Nalbuphine vs. Buprenorphine for Post-Operative Analgesia in Patients Undergoing Laparotomy under General Anesthesia

Dr. Vyshnavi Thangirala[1], Dr. Ch. Satya Venkata Teja[2]
[1](Department of Anesthesia, NRI Institute of Medical Sciences, Andhra Pradesh, India)
[2](Department of Anesthesia, NRI Institute of Medical Sciences, Andhra Pradesh, India)

Abstract:
Background*: General anesthesia is a state of controlled unconsciousness, in which medicines are used to send a patient to sleep to be unaware of surgery and not move or feel pain while it's carried out[1]. Laparotomy is a surgerythat involves incisions given through the abdominal wall to provide access into the abdominal cavity. Nalbuphine is better opioid analgesic with a lesser incidence of nausea and vomiting than Tramadol during the postoperative period.[8]Buprenorphine is an opioid agonist-antagonist or modulator with an analgesic activity 25-40 times more than morphine. The current study aims to compare the efficacy and safety of Nalbuphine Vs. Buprenorphine for post-operative analgesia in patients undergoing Laparotomy under GA.*
Materials and Methods*: In this interventional single-blinding study, 60 patients of ASA physical status I and II belonging to age group of 18-65 years undergoing elective laparotomy under general anesthesia were randomized into two groups. Each group included 30 patients.Group N patients received Nalbuphine and group B patients received Buprenorphine. randomly allocated into 2 groups of 30patients each.Time of onset of analgesia, duration of analgesia, need for rescue analgesia, side effects, visual analogue scale (VAS) scores, hemodynamic variables were assessed and compared between two groups*
Results*: There is no significant difference in age, gender, ASA grade, incidence of side effects and hemodynamic variables like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SPO2) between two groups. The mean onset of analgesia was quick in group B patients and the duration of analgesia was more in group B patients. VAS scores were significantly less in group B patients at 30 min and 60min. Rescue analgesia was not required for any patient in the current study.*
Conclusion: *Buprenorphine produced earlier onset of analgesia and prolonged duration of analgesia compared to Nalbuphine without producing any significant ADRs.Patients in Buprenorphine group were associated with lower VAS scores as compared toNalbuphine group.*
Key Words: *Nalbuphine, Buprenorphine, Post-Operative Analgesia, Laparotomy, General Anesthesia*

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I. Introduction

General anesthesia is a state of controlled unconsciousness, in which medicines are used to send a patient to sleep to be unaware of surgery and not move or feel pain while it's carried out[1].It is the responsibility of a dutiful clinician to help alleviate postoperative pain to a patient.Drugs that induce GA usually affect cortex, thalamus, reticular activating system, and spinal cord. Potential pharmacologic targets of general anesthetics are Gamma-aminobutyric acid, glutamate, and serotonin receptors[2].Ernest Guedel first introduced Guedel's[3] classification of stages of GA in 1937.Laparotomy is a surgerythat involves incisions given through the abdominal wall to provide access into the abdominal cavity. It is also called a celiotomy. *Laparotomy* is derived from Greek words "*lapara"*, meaning *flank*, and "*tomy"*, meaning *cut*[4]. 11% of the worldwide burden of disease requires surgical care or anesthesia management or both. In the United Kingdom, this is a standard procedure with approximately 30,000 to 50,000 performed annually.[5] The Lancet Commission for Global Surgery estimated that 5000 surgeries are required to meet the surgical burden of disease for 100,000 people in low- and middle-income countries including India. Indications of laparotomy include multiple dense adhesions from previous surgeries, intestinal obstruction, massive ascites, acute intraperitoneal bleeding, uncontrollable gastrointestinal bleeding, blunt or penetrating abdominal injuries, intraperitoneal sepsis, pancreaticoduodenectomy, pancreatic or intestinal transplants, etc.

One of essential injectable drugs for providing postoperative pain relief include opioid analgesics. Others include Nonsteroidal anti-inflammatory drugs (NSAIDs), like diclofenac, ibuprofen, etc.[6]Opioids, when given pre- or intraoperatively, have stimulating effects in the postoperative period as they delay recovery and

respiratory depression, sometimes necessitating ventilation.The advantage of using opioids is that they have an effective antidote named "Naloxone" to neutralize their effect, and they are more potent compared to NSAIDs. Examples of opioids commonly used after GA are Fentanyl and Morphine.Though the mainstay of postoperative analgesia is opioid based, more evidence now available to support a multimodal approach to decrease opioid side effects like nausea and ileus and improve pain scores[7]. Nalbuphine is better opioid analgesic with a lesser incidence of nausea and vomiting than Tramadol during the postoperative period.[8]Buprenorphine is an opioid agonist-antagonist or modulator with an analgesic activity 25-40 times more than morphine. It can be used for opioid deaddiction, cancer-related pain, and post-operative pain control. It has high safety profile and acts for prolonged duration of time. The drug doesn't have ceiling effect for analgesic effect[9].We hypothesize that Buprenorphine would provide more effective post operative pain control compared to Nalbuphine for laparotomies under GA.

There are already few previous studies on Nalbuphine and Buprenorphine as postoperative pain relief options in various surgeries.The current study helps to add more details to the existing research.The current study aims to compare the efficacy and safety of Nalbuphine Vs. Buprenorphine for post-operative analgesia in patients undergoing Laparotomy under GA.

II. Material And Methods

This interventional, randomized, single-blinded study was carried out at the Department of anesthesia at NRI Institute of Medical Sciences, Mangalagiri, Andhra PradeshfromDecember 2019 to October 2020.

Study Design: Interventional, randomized, single-blinded study

Study Location: This study was done at tertiary care teaching hospital in Department of anesthesia.

Study Duration: December 2019 to October 2020.

Sample size: 60 patients

Sample size calculation: The sample size was estimated on the basis of population proportion design. Around 7% of patients undergo laparotomies under general anesthesiausing Nalbuphine or Buprenorphine at our institution during the study period.

At confidencelevel of 85%, taking error as 5%, and the proportion as 7%.The minimum sample size obtained was 54. So, we included 60 patients in our study. 30 patients belonged to each group.

Subjects & selection method: The study population was drawn from patients scheduled for elective laparotomyat NRI Institute of Medical Sciences. Patients were divided into two groups (each group had 30 patients) as per the drug given.

Group N (N=30 patients) - NALBUPHINE 10mg/ml in 100ml normal saline was given to each patient;

Group B (N=30 patients) - BUPRENORPHINE 0.3mg/ml in 100ml normal saline was given by intravenous infusion to each patient.

Inclusion criteria:

1. Patients belonging to ASA grade I and II
2. Either sex
3. Aged 18-65 years,
4. Patients undergoing elective laparotomy under general anesthesia.

Exclusion criteria:

1. Pregnant and lactating women
2. Patients with cardio-pulmonary disorders
3. Patients with Physical dependence on opioids
4. Patients with Known allergies to the medications used.
5. Patients with severe hepatic and renal disorders

Methodology:

Patients were randomized into two groups using computer-generated number table. Pre anesthetic assessment is done 24 hours before surgery.Informed consent is taken from every patient. All 60 patients accepted to participate in this study and gave written ICF.All the patients underwent proper physical examination and required blood testing. Medical history was taken from all patients as per the case record form (CRF).The patients who were involved in randomization and drug preparation doesn't know the information about the type of drug that was given to them (single-blinded).We have used 10-point scale to identify the severity of pain among patients. All the patients were asked to fast for at least six hours before the surgery. In the surgery room, we monitored patient's electrocardiograph (ECG), heart rate (HR), oxygen saturation (SpO2) and blood pressure. Baseline vital parameters were also assessed. Premedication with Alprazolam 0.5mg is given one night before surgery. Alprazolam is a benzodiazepine that decreases apprehension-it acts by

increasing Inhibitory CNS neurotransmitter gamma-aminobutyric acid (GABA).After shifting the patient to the operation theatre (OT), monitors were connected, and IV line was secured. After administration of inj. Glycopyrrolate(5mcg/kg), inj. Midazolam (0.03mg/kg) and inj. Fentanyl (2mcg/kg) patient was induced with inj. Propofol (2mg/kg). inj. Vecuronium (0.1mg/kg) administered to facilitate muscle relaxation. Endotracheal intubation was performed and anesthesia was maintained using sevoflurane (0.2-1%), nitrous oxide, and oxygen. At the end of surgical procedure Neuromuscular blockage was reversed with inj. Neostigmine (0.05mcg/kg) and inj. Glycopyrrolate (10mcg/kg).

The prescribed doses of medications were as follows:
Patients randomly received either NALBUPHINE (10mg/ml) or BUPRENORPHINE (0.3mg/ml) intravenously in a drip of 100ml normal saline over 15 to 20 min and were allocated into Buprenorphine Group-B or Nalbuphine group-N. Intravenous paracetamol is used as a rescue analgesia depending on the visual analog scale (VAS) pain score of >6

Ethical considerations:
Permission was obtained from the Institutional ethical committee attached to NRI medical college was taken before conducting the study. Every patient was explained the whole process and advantages of the study. After he/she accepts, an informed consent form is given in local language or patient understandable language and the person was asked to sign it or put a thumb impression.

Statistical analysis
Data was analyzed using Epi info software version 7.2.5. Student's *t*-test was used to compare numerical parameters between two groups. P value <0.05 was considered significant.

III. Results

The current study included 60 patients divided into groups B and N.

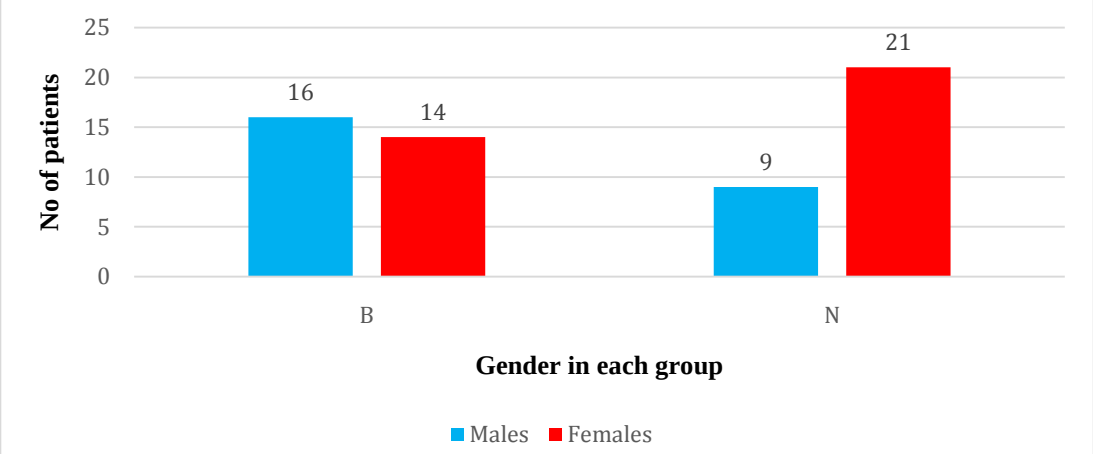
Age: Table no 1 shows age distribution of patients in each group. There is no significant difference in the mean age of patients of both groups, as per T test. Hence the comparison is justifiable without age-related bias.

Table no 1: Shows mean age of patients in both groups.

Age group * Drug					P value
		Drug			
		B	N	Total	
Age group	<20	5	2	7	0.4
	21-30	4	9	13	
	31-40	12	9	21	
	41-50	8	8	16	
	>50	1	2	3	
Total		30	30	60	

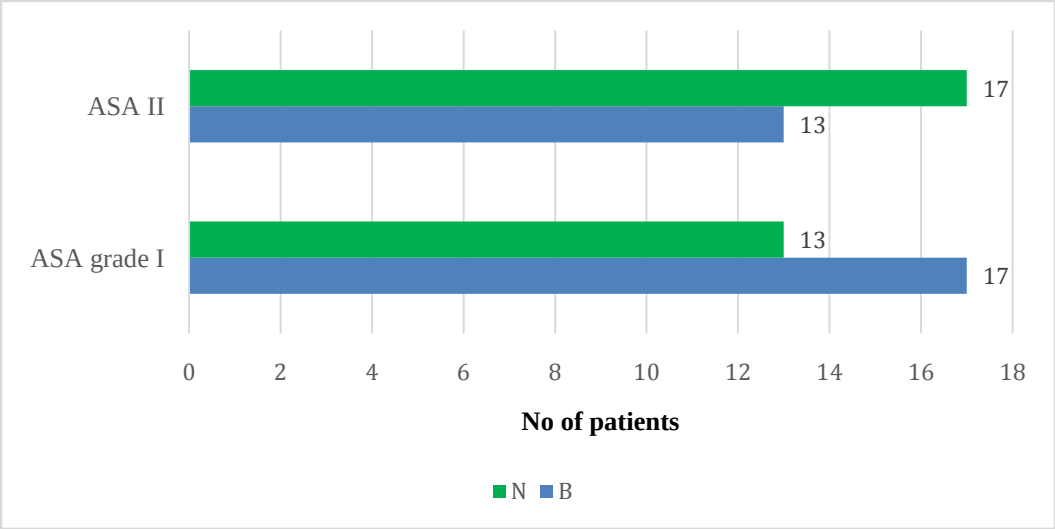
Gender: There is no significant difference in gender distribution between two groups, as per chi square analysis(p=0.06). Graph 1 shows gender distribution in each group.

Graph 1: Gender distribution



ASA grade: There is no significant difference in ASA grade in both groups(p=0.3).

Graph 2: ASA distribution among study patients



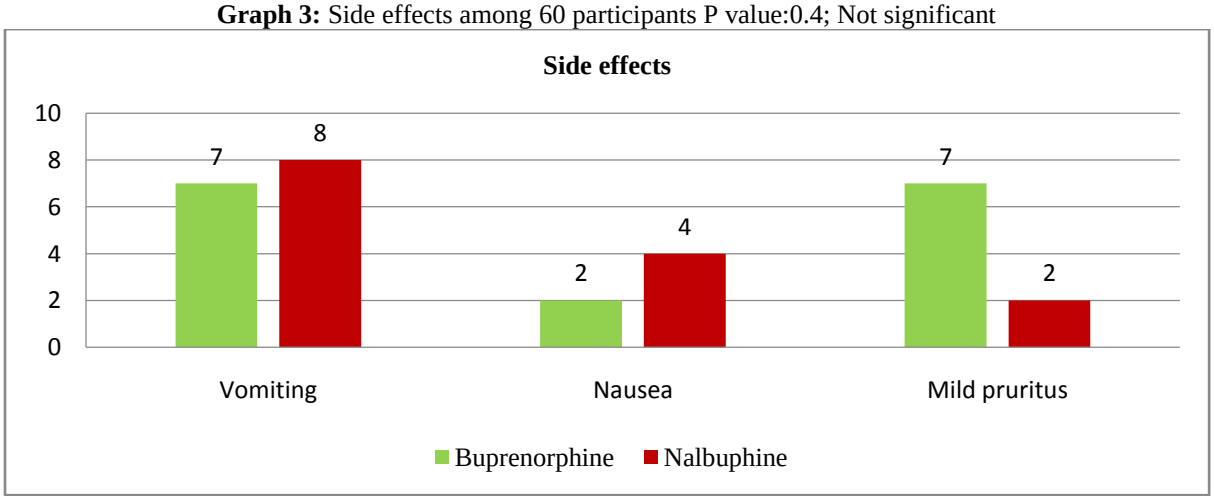
Onset, duration of analgesia and VAS scores: Onset of analgesia is quick in B group patients. Duration of analgesia was significantly more in B group patients. There is no significant difference in mean VAS scores between two groups of patients at baseline at the score was significantly less in group B at 30 and 60 min.

Table 2 shows onset, duration of analgesia and VAS scores

Parameters	Group B	Group N	P value
Onset of analgesia	23.8±1.03 min	27.4±1.47 min	< 0.0001
Duration of analgesia	322.36± 28.5 min	280.2±26.6 min	< 0.0001
VAS at baseline	7.0±0.9	6.93±0.69	0.52
VAS at 30 min	3.0±0.17	6.0±0.63	< 0.0001
VAS at 60 min	0.6±1.8	4.7±0.72	< 0.0001

Rescue analgesia: No subject required rescue analgesia in our study.
Side effects: Graph 3 shows side effects of drugs buprenorphine and nalbuphine among 60 patients.
30 patients didn't complain any side effects. Nausea and vomiting are slightly common in Nalbuphine group. Pruritis was more common in Buprenorphine group. There was no respiratory depression or sedation in patients of either group.

Graph 3: Side effects among 60 participants P value:0.4; Not significant



Hemodynamic parameters: There are no significantdifferences in heart rate, systolic, diastolic blood pressure (SBP and DBP), and oxygen saturation in both groups at baseline, 15min, 30min and 45 min.

Table 3 shows hemodynamic parameters in both groups

Parameters	Buprenorphine	Nalbuphine	P Value
Heart rate at Baseline	80.767±6.4577	78.600±6.9808	0.217
HR 15 min	77.100±6.3046	74.833±6.6076	0.179
HR 30 min	76.267±5.9766	74.200±5.8804	0.182
HR 45 min	77.067±6.4001	75.933±6.0795	0.485
SBP at baseline	126.667±7.8798	128.667±8.5433	0.350
SBP at 15min	124.767±8.1735	125.967±9.4922	0.602
SBP at 30 min	124.533±7.7492	125.967±7.8630	0.480
SBP at 45 min	124.967±7.7792	126.600±8.3236	0.436
DBP at baseline	77.167±7.8393	78.533±8.1610	0.511
DBP at 15 min	74.233±6.3500	75.733±7.2774	0.398
DBP at 30 min	75.367±7.6315	76.333±6.9844	0.611
DBP at 45 min	76.067±6.6485	76.100±7.2176	0.985
Spo2 at baseline	98.3±1.3%	97.8±1.2%	0.325
SPO2 at 15 min	96.63±1.3%	96.96±1.4%	0.31
SPO2 at 30 min	97.2±1.3%	97.2±1.1%	0.84
SPO2 at 45 min	97.96±1.2%	98.0±1.3%	0.92

IV. Discussion

In the current study, 30 patients received Nalbuphine (Group N) and 30 patients received Buprenorphine (Group B) for post operative analgesia after general anesthesia for laparotomies.

Buprenoprhine is a partial agonist-attaching ability to opioid receptors is less compared to full.[10]Nalbuphine acts by binding to mu and kappa opioid receptors to provide pain relief.[11]

Most of the patients were around 31-40 years of age. 30 patients belonged to ASA grade I. Among them, 17 patients belonged to B group and 13 patients belonged to N group.17 patients belonged to ASA grade II in Nalbuphine group, and 13 patients belong to ASA grade II in Buprenorphine group.The onset of analgesia is faster in Buprenorphine group compared to Nalbuphine group and the difference is significant. Also, the duration of analgesia is more in Buprenorphine group compared to Nalbuphine group. 30 patients didn't complain any side effects. Nausea and vomiting are slightly common in Nalbuphine group. Pruritis is more in Buprenorphine group. VAS score was significantly less in group B compared to group A. There are no significant differences in hemodynamic variables between two groups at baseline to 45min.

In S Babu's study**[12]**, a comparison was done between epidural Ropivacaine with Nalbuphine and ropivacaine with Butorphanol in 80 patients. It was observed that ropivacaine with Nalbuphine group had good quality of analgesia and stable cardiorespiratory parameters. The need of rescue analgesia was higher in the ropivacaine Buprenorphine group during the first 6 h. Epidurally administered ropivacaine with Nalbuphine is more effective compared to ropivacaine with butorphanol for PO pain relief in patients undergoing emergency laparotomy. In the current study, IV Buprenorphine was found to be more effective than Nalbuphine for post-operative analgesia.

In the Minai's study**[13]**, Nalbuphine was compared to another opioid-morphine. Both were administered intraoperatively before intubation andhemodynamic stability, intraoperative analgesia, recovery profiles, incidence of side effects and need for postoperative supplements were compared in total abdominal hysterectomies done on fifty patients. Patients in the morphine group had a rise of mean blood pressure and heart rate to 20% above the baseline in response to intubation and postoperative supplements was significantly less in the nalbuphine group.

In Vaidyanathan B et al.[14] study Buprenorphine versus Intravenous Morphine were compared as premedicant and postoperative analgesic in patients undergoing laparoscopic appendectomy under general anesthesia. A total of 110 patients undergoing laparoscopic appendectomies were randomized into two groups. Group B patients received 0.4 mg of buprenorphine tablet sublingually 1h before surgery and group M patients received 0.1mg/kg of intravenous morphine 10min before anesthesia induction. Intraoperative vitals, heart rate and mean arterial pressure were significantly stable in group B compared to group M. Only 11 % patients in group B required dexmedetomidine infusion compared to 37% in group M, to control intraoperative hypertension. Visual analog scale (VAS) values in group B at 2nd (1.30 ± 0.46), 4th (1.31 ± 0.54), and 6th hour (1.33 ± 0.63) were significantly less than group M. Sublingual buprenorphine premedication is an alternative to intravenous injection of morphine with perioperative hemodynamic stability and better postoperative analgesia. In our study, IV Buprenorphine was compared with IV Nalbuphine. The onset of analgesia is faster, and the duration of analgesia is longer in the Buprenorphine group for post operative analgesia

In X Liu's study[15] , 2094 participants scheduled for laparoscopic cholecystectomy were randomly assigned to receive nalbuphine (Nal group, n = 1029) or placebo (Con group, n = 1027). The Nal group received IV Nalbuphine 0.2 mgkg-1 and the Con group received saline. Nalbuphine reduced the visceral pain both at rest (b = - 0.1189, 95% CI - 0.23 to - 0.01, P = 0.037) and movement (b = - 0.1076, 95% CI - 0.21 to - 0.01, P = 0.040) compared with placebo. Patients in the Nal group required less frequent supplemental analgesic administration during the first 24 h after surgery. Like our study, nausea and vomiting are seen in few patients in the Nalbuphine group. In FA Khan's study**[16]**,IV Nalbuphine (0.3 mg.kg-1) was compared with IV Buprenorphine (2.5 micrograms.kg-1) as part of a total intravenous anesthesia regimen using a propofol infusion in 60 patients undergoing laparoscopic cholecystectomy. The results showed no difference was observed in blood pressure, but the heart rate was significantly lower in the Buprenorphine group. Recovery was fast and comparable with both drugs, and no patient reported awareness. Quality of analgesia was similar in both groups. Both drugs provide suitable analgesic supplementation to total intravenous anesthesia in Khan's study. In contrast, in our study, there is no significant difference in hemodynamic parameters in Buprenorphine and Nalbuphine groups and Buprenorphine was found to be better in terms of efficacy and safety compared to Nalbuphine group.

In the study of Srishti Tiwari[17] 60 patients with A.S.A. physical status I and II of patients aged 18-60 years undergoing lower limb surgery were included. Group A received Bupivacaine, and Nalbuphine and Group B received Bupivacaine and Buprenorphine. Postoperative pain relief is significantly longer in Buprenorphine group compared to Nalbuphine group with Bupivacaine.

Kiran K et al.[18]did a study on patients undergoing elective surgeries done under general anesthesia. 60 patients with moderate to severe pain received either nalbuphine in the dose of 10mg or either Tramadol in the dose of100 mg. Subjects received nalbuphine or Tramadol. They concluded that nalbuphine and Tramadol could provide effective pain control.

V. Conclusion

Buprenorphine produced earlier onset of analgesia and prolonged duration of analgesia compared to Nalbuphine without producing any significant ADRs.

Patients in IV Buprenorphine group were associated with low VAS scores as compared to Nalbuphine group. Buprenorphine gives better post operative analgesia than Nalbuphine after general anaesthesia in patients undergoing laparotomies.

The study is self-sponsored and there are no conflicts of interest.

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