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Comparison of efficacy of butorphanol and nalbuphine as premedicant in patients undergoing elective craniotomy using propofol and desflurane anesthesia – A randomized clinical study

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ABSTRACT

Background: Long duration neurosurgical procedures require the use a relatively longer acting analgesic which will give equianalgesia like a short-acting opioid without needing repeated administration or an infusion. **Aims and Objectives:** In this study, we investigated and compared the intraoperative analgesic efficacy and post-operative recovery outcome of intravenous (IV) butorphanol and IV nalbuphine in non-emergency craniotomy patients. **Materials and Methods:** A prospective, randomized, and double-blind study was conducted involving 60 patients of age 18–50 years, randomly assigned into two equal groups receiving either 1 mg butorphanol IV (Group B) or 10 mg nalbuphine IV (Group N) 10 min before induction of general anesthesia. Patients were monitored for changes in blood pressure, heart rate (HR) perioperatively and duration of analgesia, and Ramsay Sedation Score (RSS) postoperatively. The results were recorded and analyzed statistically using Pearson's Chi-square test for Independence of Attributes/Fisher's Exact Test and Student's t-test for continuous variables. **Results:** Statistically significant fall in HR and mean blood pressure was seen in both groups during intraoperative period, though fall was more in the nalbuphine group. Duration of analgesia was statistically significant in Group B than Group N (249.27 ± 18.33 vs. 240.13 ± 15.70, P = 0.043). Sedation was more with nalbuphine as time to achieve RSS 2 was less with butorphanol. **Conclusion:** Inj. butorphanol and inj nalbuphine both showed satisfactory result in maintaining hemodynamic stability and long duration of analgesia. When compared, butorphanol provided longer duration of analgesia and less post-operative sedation.

Key words: Anesthesia; Craniotomy; Opioid; Recovery; Sedation

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INTRODUCTION

Premedication refers to the administration of drug before induction and maintenance of anesthesia.[1] An ideal premedicant drug should be an anxiolytic, sedative and amnestic, should reduce salivary and respiratory tract secretions, and provide perioperative analgesia.[2,3] Concern regarding recovery profile after surgery is gaining momentum as current practice of enhanced recovery after surgery is becoming widely recognized. Usually in neurosurgery, short-acting opioids such as fentanyl, alfentanil, and remifentanil are being used as analgesic which are needed to be repeated at regular interval.[4-6] Long-acting opioid analgesic would be a better alternative with the view of better control of pain and reducing the need of repeated dose at regular interval.

Although morphine like alkaloids have been used for centuries, the problem with these drugs are respiratory

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depression, addiction, nausea, and vomiting. These side-effects are overcome by the introduction of mixed agonist antagonist opioid analgesics such as butorphanol, nalbuphine, and pentazocine.[7]

Butorphanol and nalbuphine are synthetic mixed agonist antagonist opioid analgesic. These drugs have the advantage of easy availability, lesser side effects than morphine in terms of nausea, vomiting, respiratory depression, and addiction. Moreover, these mixed agonist antagonist produce neither pruritus nor urinary retention. These drugs provide adequate analgesia with no or minimal cardiovascular changes.[8-10]

Propofol is nowadays most commonly used intravenous (IV) anesthetic agent with favorable pharmacokinetic profile.[11,12] It is preferred in neurosurgery as it causes a dose dependent decrease in intracranial pressure (ICP) maintaining cerebral perfusion at modest dose. It also reduces cerebral metabolic rate without any disturbances in cerebral reactivity to carbon dioxide and autoregulation.[11]

Early neurological assessment is essential following most neurosurgical operations. Thus, it is prudent to use drugs and techniques which should not cause any hindrance to this objective. Hence, choice of anesthetics and techniques should always fulfill this prime objective while anesthetizing these patients. Nowadays, volatile, potent, and inhalational anesthetics are the agent of choice for maintenance of general anesthesia. Although desflurane theoretically raises concern due to its capacity to cause cerebral vasodilatation, different studies have shown that changes in ICP and cerebral blood flow are similar in desflurane and isoflurane.[13,14] Hence, desflurane is a better choice as it significantly reduces emergence time. Desflurane provides rapid recovery due to its lower blood gas solubility. In a dose of <l MAC value, it causes no detrimental effects on cerebrovascular system.

Aims and objectives

There is paucity of studies regarding intraoperative conditions and patient outcomes in neurosurgical patients with butorphanol/nalbuphin with propofol and desflurane. Accordingly, this present study was planned with the primary objective to compare the recovery profile and secondary objective to compare the analgesic efficacy and cardiovascular effects of butorphanol and nalbuphine as premedicant with propofol and desflurane anesthesia in non-emergency craniotomy surgeries.

MATERIALS AND METHODS

This prospective, randomized, double-blinded, and comparative study was conducted at Calcutta National Medical College and Hospital, Kolkata, West Bengal India for 1 year (January 2019–December 2019). The Institutional Ethics Committee clearance was taken before conduct of the study.

Sample size was calculated in consultation with a statistician and based on the previous studies which indicated that approximately 25 patients should be included in each group to ensure power of 80% and α-error of 0.05 for detecting clinically significant difference in mean arterial pressure and duration of analgesia by 20% among study groups.[15,16] Assuming a 5% drop out rate and for equal distribution of patients, a total of 60 patients were recruited for the present study.

Inclusion criteria – patients belonging to American Society of Anesthesiologists (ASA) physical status I and II, and age range 18–50 years undergoing elective neurosurgical procedure requiring general anesthesia with Glasgow Coma Scale 13 and more were chosen for the study. Exclusion criteria – patient refusal, ASA physical status III and above, age below 18 years and above 50 years, those with any anticipated difficult airway, history of allergy to any of the study drugs, psychiatric illness, and alcohol abuse were excluded from the study. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients. A senior, experienced anesthesiologist was always present during the course of the study for managing any untoward events.

Study technique

All the patients were kept nil per oral for 8 h before surgery. On arrival in the operating room, an IV cannulation was done and baseline heart rate (HR), mean blood pressure (MBP), and oxygen saturation (SpO_2) were recorded. All patients were premedicated with inj. midazolam 0.03 mg/kg and inj. glycopyrrolate 1 ml containing 0.2 mg. The patients were randomly assigned to one of the two groups. Group B (n=30) received 1 mg of butorphanol IV 10 min before induction. Group N (n=30) received 10 mg of nalbuphine IV 10 min before induction.

Each drug was pre-set to five ml of total volume mixed with normal saline and syringes were labeled as study drug by the observer. The calculated dose of the study drug was given by the fellow anesthesiologist without knowledge of the drug's identity 10 min before induction with propofol. After pre-oxygenation, induction of anesthesia was done with injection propofol 2 mg/kg followed by injection vecuronium 0.1 mg/kg IV. The intubation was done with proper size flexometallic cuffed endotracheal tube after proper relaxation.

HR per minute, MBP in mm Hg, and SpO_2 were noted before premedication and at 3, 5, and 10 min after

premedication and study drug administration and after induction and intubation. Maintenance of anesthesia was done with 0.5 MAC of desflurane in oxygen and nitrous oxide. Intermittent doses of vecuronium bromide were given in both the groups as and when required. Ventilation was adjusted to keep the end tidal carbon-oxide in the range of 30–35 mm of Hg. The anesthetic agent desflurane was stopped after skull pin site closure in all patients. All the patients were monitored throughout the operation.

HR and MBP were recorded every 5 min until 15 min, then every 15 min until 90 min, then every half hourly until the completion of surgery, and then in the post-operative period until the demand of post-operative analgesics. Reversal was done after completion of surgical procedure. Patients were given injection neostigmine in a dose of 0.05 mg/kg with injection glycopyrrolate 0.01 mg/kg after beginning of respiratory efforts. All patients were extubated on the operating table after recovery of adequate spontaneous respiration with adequate tidal excursion. The time interval between cessation of the anesthetic agent, extubation, and recovery of consciousness after extubation were recorded.

In the recovery room, the patients were assessed for Ramsay Sedation Score (RSS), post-operative nausea vomiting, and duration of analgesia.

RSS was used in the post-operative room for assessment of sedation (Score 1 = Anxious, agitated, non-cooperative; Score 2 = Cooperative, oriented, tranquil; Score 3 = Respond to verbal commands; Score 4 = Brisk response to loud noise or a light tap; Score 5 = Sluggish response to loud noise or a light tap; and Score 6 = No response to stimuli).

RSS was noted at every 5 min interval until the patient reached the sedation score of 2, which was considered to be acceptable as at score two patients were cooperative and tranquil.

Statistical analysis

Data were entered in the Microsoft Excel and analysis was performed using the Statistical Package for the Social Sciences for Windows, Version 20.0 software (IBM, Bengaluru, India). Categorical variables were expressed as number of patients and percentage and compared across the groups using Pearson's Chi-square test for Independence of Attributes/Fisher's Exact Test as appropriate. Continuous variables were expressed as mean, median, and standard deviation and compared across the groups using Student's t-test. An alpha level of 5% has been taken, that is, if any $P<0.05$, it has been considered as significant.

RESULTS

A total 78 patients were screened and 60 patients meeting the inclusion criteria and willing to participate in the study were randomized into two groups (Figure 1).

Study groups were comparable with respect to age, height, weight, sex, and ASA grade. There was no statistically significant difference in their demographic profile (Table 1).

Statistically significant fall in HR and MBP during intraoperative period and immediate post-extubation period which were seen in both groups, which was more in the nalbuphine group (Tables 2 and 3).

Duration of surgery and time to extubation among two groups showed no statistically significant difference (Table 4). Duration of analgesia was statistically significant when Group B and Group N were compared, which was prolonged in butorphanol group (249.27±18.33 vs. 240.13±15.70, P=0.043) (Table 4). Sedation was more with nalbuphine (502.53±46.06 vs. 201.57±52.61) and time to achieve RSS 2 was less with butorphenol (22.43±2.97 vs. 27.60±2.21) (Table 4).

Post-operative nausea and vomiting among two groups showed no statistically significant difference (Table 5).

DISCUSSION

The use of IV narcotics in balanced anesthesia is a well-recognized technique.[5] The present study demonstrated that butorphanol and nalbuphine as synthetic agonist antagonist opioid analgesic provided acceptable hemodynamic stability and good analgesia in neurosurgical patient. Regarding post-operative recovery, butorphanol scored better producing less sedation and early achievement of RSS 2.

There are limited studies on the comparison of butorphanol and nalbuphine use in neurosurgery. One of the objective specific to neurosurgery is to achieve an early recovery after anesthesia to facilitate the neurological evaluation of the patient. Hence, narcotics with less delayed awakening postoperatively are preferred.

The present study showed significant fall in MBP and HR following premedication with the study drugs (butorphanol or nalbuphine) and propofol induction in both the groups (Tables 2 and 3). In Group N, fall in hemodynamic parameters was statistically significant than Group B. Sympathetic response of laryngoscopy and intubation was suppressed in both the groups. This attenuation of hemodynamic and somatic response to

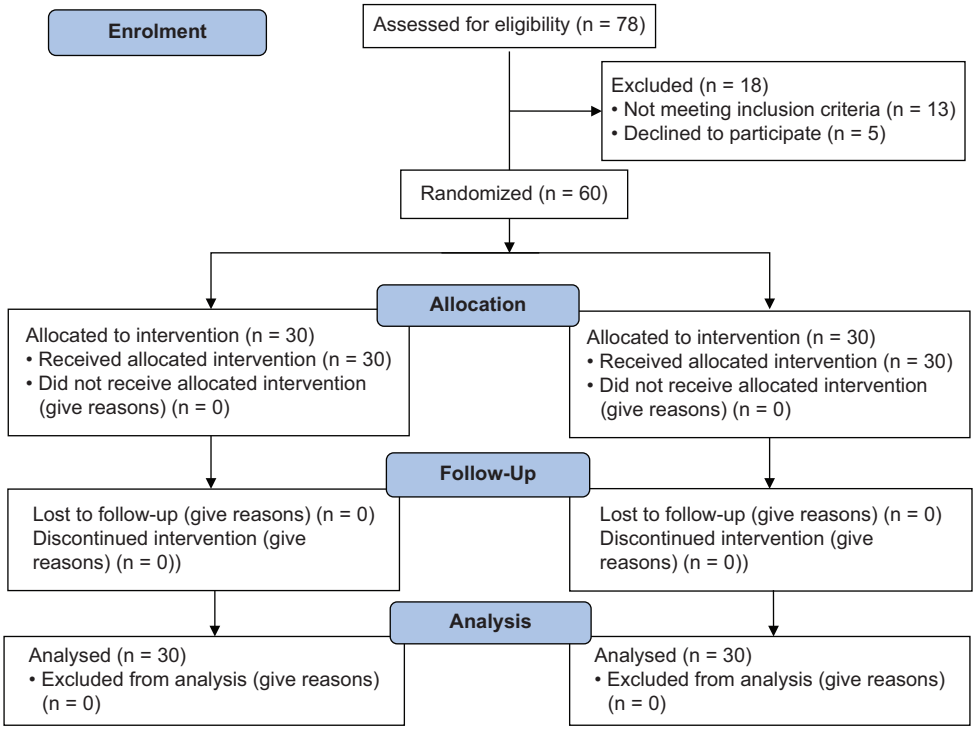

Figure 1: Consort flow chart showing division of patients at every stage of trial

Table 1: Comparison of demographic variables between study groups

Demographic variables	GROUP-B n=30	GROUP-N n=30	P-value
Sex (Male: Female)	16:14	15:15	1.000**
Age (Years)	40.07±3.40	39.97±3.1	0.906*
Body weight (kg)	55.63±4.54	55.07±4.27	0.620*
Height (cm)	160.03±10.36	161.63±9.41	0.705*
ASA grade (I: II)	24:6	24:6	0.936**

Data entered as mean±standard deviation, n=number of patients P-values calculated using *Student's t-test and **Chi-square test; P<0.05 considered statistically significant

Table 2: Comparison of pre-operative, intraoperative, and post-operative heart rate (HR) per minute among study groups

Time Interval	Group B (n=30) (Mean±SD)	Group N (n=30) (Mean±SD)	P-value*
Baseline	82.00±8.18	83.67±5.24	0.351
Post medication at 3 min	79.07±7.12	79.40±6.66	0.852
Post medication at 5 min	77.43±6.80	77.90±6.57	0.788
Post medication at 10 min	73.70±5.65	74.73±6.68	0.520
Post-induction	71.33±7.53	71.77±7.53	0.824
Post-intubation at immediately	84.60±7.76	85.30±6.43	0.705
After 5 min	85.53±5.57	83.47±6.06	0.174
After 10 min	85.13±6.24	80.83±7.62	0.020
After 15 min	85.30±6.34	78.30±8.23	<0.001
After 30 min	82.60±7.70	74.80±8.51	<0.001
After 45 min	80.03±7.92	72.13±8.44	<0.001
After 60 min	77.47±7.54	68.53±6.75	<0.001
After 90 min	76.77±7.58	66.67±7.22	<0.001
After 120 min	74.53±7.04	66.30±7.24	<0.001
After 150 min	73.53±6.52	69.63±8.57	0.052
After 180 min	75.52±8.57	71.23±5.98	0.063
Post-extubation	81.23±6.20	75.97±4.76	<0.001

SD: Standard deviation, n=Number of patients P-values calculated using *Student's t-test; P<0.05 considered statistically significant

laryngoscopy and endotracheal intubation was attributed to the following reasons: firstly sedation and analgesia caused by butorphanol and nalbuphine and secondly by the direct myocardial depressant effect and sedation by propofol. MBP in both the groups in the present study was within normal clinical limit. Usually after 90 min of operation, the values of two groups became almost similar (Table 3). Hence, it might be stated that both butorphanol and nalbuphine were able to blunt the hemodynamic response when used with propofol. This is an advantageous factor in procedures related to neurosurgery. Chawda et al., found that nalbuphine (0.2 mg/kg) prevented rise of HR and MBP following laryngoscopy and endotracheal intubation when administered 5 min before laryngoscopy.[15] Various studies found butorphanol as a safe intraoperative analgesic in neurosurgical patients with statistically better hemodynamics and earlier recovery when used with propofol as compared to thiopentone-isoflurane anesthesia.[16,17] Sharma and Parikh found that nalbuphine and fentanyl were to be better than tramadol in case of attenuation of

Table 3: Comparison of pre-operative, intraoperative, and post-operative mean blood pressure (MBP) in mm of Hg among study groups

Time Interval	Group B (n=30) (Mean±SD)	Group N (n=30) (Mean±SD)	P-value*
Baseline	98.30±5.36	97.93±5.89	0.802
Post-medication at 3 min	94.90±5.29	94.53±5.32	0.790
Post-medication at 5 min	94.67±4.77	91.53±4.52	0.011
Post-medication at 10 min	95.57±5.02	89.60±4.99	<0.001
Post-induction	89.77±5.06	84.50±7.09	0.002
Post-intubation at immediately	104.97±5.70	93.93±6.27	<0.001
After 5 min	106.90±6.09	95.50±5.58	<0.001
After 10 min	103.37±6.17	93.53±3.90	<0.001
After 15 min	95.00±6.37	90.60±4.45	0.003
After 30 min	96.53±5.22	89.40±5.68	<0.001
After 45 min	97.27±5.35	88.20±5.10	<0.001
After 60 min	97.20±6.22	87.10±5.28	<0.001
After 90 min	96.17±5.07	88.30±4.69	<0.001
After 120 min	95.10±4.42	90.97±4.85	0.001
After 150 min	94.70±4.52	92.60±4.42	0.074
After 180 min	96.86±5.14	93.05±4.41	0.012
Post-extubation	102.33±4.37	98.17±4.16	<0.001

SD: Standard deviation, n=number of patients P-values calculated using *Student's t-test; P<0.05 considered statistically significant

Table 4: Comparison of duration of surgery, time to extubation, time to gain consciousness, and achieve RSS 2 and duration of analgesia among study groups

Criteria	Group-B n= 30 (Mean±SD)	Group-N n= 30 (Mean±SD)	P-value*
Duration of surgery (minutes)	184.03±9.47	184.97±11.48	0.733
Time to extubation (seconds)	449.20±76.68	443.60±79.76	0.443
Time to gain consciousness (seconds)	201.57±52.61	502.53±46.06	<0.001
Time to achieve Ramsay Sedation Score 2 (minutes)	22.43±2.97	27.60±2.21	<0.001
Duration of analgesia (minutes)	249.27±18.33	240.13±15.70	0.043

SD: Standard deviation, n= number of patients P-values calculated using *Student's t-test; P<0.05 considered statistically significant

hemodynamic response to laryngoscopy.[8] All these published articles strengthened present study findings.

Deep plane of anesthesia was maintained in our study by muscle relaxant vecuronium and volatile agent desflurane. Toward the end of anesthesia in both groups, HR and MBP were gradually increased. This increase could be due to lighter plane of anesthesia toward the end of surgery.

Table 5: Comparison of post-operative nausea and vomiting (PONV) among study groups

PONV	Group B (n=30)	Group N (n=30)	P-value**
Absent	27	28	0.640
Present	3	2	

n=number of patients P-values calculated using **Chi-square test; P<0.05 considered statistically significant

In the present study, duration of anesthesia was statistically insignificant (P=0.733), but duration of analgesia was statistically significant (P<0.05) when both groups were compared (Table 4). Agarwal et al., observed the pain relieving property of butorphanol when given as premedication before IV propofol.[18] Patel and Kantharia concluded in their study that post-operative analgesia was significantly more (up to 180 min) in the butorphanol group; 82% patient of fentanyl group had pain by 30 min in the post-operative period, whereas none of the patient of butorphanol group had significant pain by 30 min.[3] Nalbuphine also showed good hemodynamic control and excellent post-operative analgesia when compared with fentanyl with less frequent dosing.[19] A recent randomized study concluded that inj. butorphanol 20 μg/kg was more efficacious when compared to inj. nalbuphine 0.2 mg/kg as an analgesic for use in laparoscopic surgeries due to its ability to produce prolonged analgesia and better hemodynamic stability.[20] These studies along with present study completely justified the use of long-acting opioids in neurosurgical patients.

The time to achieve RSS 2 and time to gain consciousness were statistically significant when both groups were compared (Table 4). This showed that sedation was an inescapable aftereffect of both butorphanol and nalbuphine when given in therapeutic doses. However, in our study, it was more with nalbuphine than butorphanol. Verma and Jaiswal also found in their study that unavoidable side-effect of butorphanol was sedation.[21] The incidence of post-operative nausea and vomiting was minimal in both the groups and was statistically insignificant (Table 5).

Limitations of the study

The depth of anesthesia could not be monitored due to unavailability of bispectral index monitoring system or entropy.

CONCLUSION

The study provides compelling evidence justifying the role of inj. butorphanol 1mg and inj. nalbuphine 10 mg as efficacious premedicants for use in neurosurgery with propofol and desflurane. Wherein the study infers the better role of inj. butorphanol as compared to inj. nalbuphine in

terms of hemodynamic stability, duration of analgesia, lesser post-operative sedation, and satisfactory recovery profile.

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Authors Contribution:
TP- Concept and design of the study, statistical analysis, interpreted the results, prepared first draft of manuscript; **CB**- Concept, reviewed the literature, statistical analysis, interpretation and manuscript preparation; **SBK**- Coordination, preparation of manuscript and revision of the manuscript

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