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A COMPARATIVE STUDY OF BUTORPHANOL AND NALBUPHINE USING PROPOFOL AND ISOFLURANE IN PATIENTS UNDERGOING ELECTIVE CRANIOTOMY UNDER GENERAL ANAESTHESIA

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ABSTRACT

Early neurological assessment is essential following most neurosurgical operations. Thus we need to use drugs and techniques that should not cause any hindrance to this objective. This study compared the analgesic efficacy, cardiovascular effects, recovery profile and complications of premedication with Butorphanol and nalbuphine in the intra and immediate postoperative period. Sixty patients underwent craniotomy were included in this study and they were randomly divided into two groups of 30 each. Group A patients received butorphanol (2mg) IV and group B received nalbuphine (10 mg) IV ten minutes prior to intubation, followed by slow injection of 30μg/kg midazolam. All were assessed for sedation, postoperative nausea and vomiting (PONV) in the recovery room. We found that use of analgesics butorphanol 2 mg in group A and Nalbuphine 10 mg in group B provided haemodynamic stability and no incidence of PONV as a component of balanced anaesthesia in craniotomy surgery. Sedation is unavoidable side effect of both Butorphanol and nalbuphine when given in adequate doses. After extubation Ramsay sedation score-2 was achieved at 90 minute in group A (Butorphanol) and 75 min in group B (nalbubuphine). The demand of analgesic in postoperative period was at 4 hrs in group A (butorphanol) and 5.5 hrs in group B (nalbuphine) (P<0.05, significant).

Keywords: Butorphanol, Nalbuphine, Premedication, Craniotomy

INTRODUCTION

As most of the neurosurgical procedures are of longer duration, it is quite reasonable that we use a relatively longer acting analgesic which can give an equianalgesic intra operative period than a shorter acting newer opioid which needs to be repeated frequently or given by continuous infusion. On the other hand, early neurological assessment is essential following

most neurosurgical operations. Thus we need to use drugs and techniques that should not cause any hindrance to this objective. Propofol and Isoflurane have well proven roles as intravenous and inhalational anaesthetics respectively in neurosurgery[14]. Butorphanol has been reported to provide adequate analgesia when used as a supplement in balanced anaesthetic technique[3]. In healthy volunteers, Butorphanol (0.03-0.06mg.kg-1 IV) produces no or minimal cardiovascular changes[11]. Also Nalbuphine which lack of cardiac depression[12] and a ceiling effect on respiratory depression[18], make it appear to be potentially suitable as an analgesic component in balanced anaesthesia. Nalbuphine does, however, reduce the mean alveolar concentration of inhalation anesthetics[4,6]. The opioid agonist-antagonist drugs (like Butorphanol and Nalbuphine) produce mixed actions at the opiate receptor level, theoretically providing analgesia (agonist property) with lesser side effects (antagonist properties), but also exhibit ceiling effects.

OBJECTIVES

1. To compare the analgesic efficacy and cardiovascular effects of the Butorphanol, with equianalgesic doses of the Nalbuphine in the intraoperative and immediate postoperative period.
2. To compare the recovery profile of the Butorphanol, with equianalgesic doses of the Nalbuphine during postoperative period.
3. To compare the incidence of PONV of the Butorphanol, with equianalgesic doses of the Nalbuphine.

REVIEW OF LITERATURE

Thomas J. Pallasch, Clarie J. Gill (1985)[20], found that Butorphanol and Nalbuphine both drugs are equianalgesic (and nalbuphine is equipotent) with morphine parenterally and codeine orally. Their pharmacokinetics is similar; nalbuphine has a longer duration of action. Both may precipitate abstinence syndrome in narcotic-dependent persons and will probably be associated with low-level drug abuse potential. They are both agonists of the kappa opioid receptors and partial agonists of the mu receptors. Butorphanol is a partial agonist of the sigma receptor responsible for psychotomimetic effects. The incidence of adverse effects is less, sedation being the most common. In cardiac-risk patients, nalbuphine does not increase cardiac work or oxygen requirements; nor do increasing doses of nalbuphine increase the duration of respiratory depression. Both drugs possess plateau respiratory depressant actions.

F. N. Minai and F. A. Khan (2003) [13], they compared morphine and nalbuphine for intraoperative and postoperative analgesia. They concluded that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater hemodynamic stability, as a component of balanced anaesthesia in lower abdominal surgery, with a lower incidence of nausea and vomiting in the postoperative period compared to morphine 0.1 mg/kg. The duration of analgesia with Nalbuphine was significantly longer, reducing the need for supplements in the immediate postoperative period.

R.K. Verma, S. Jaiswal, et al. (2007)[22], they compared butorphanol and fentanyl as total intravenous anaesthesia in laparoscopic cholecystectomy. In this study sixty patients were allocated to one of the two groups of 30 each. Group I received inj. fentanyl 2 µg/kg while patients in group II received butorphanol 25µg/kg. All the patients were induced with inj.

propofol 2mg/kg and muscle relaxation with 100µg/kg vecuronium. Anaesthesia was maintained by oxygen and propofol infusion. Intra-operative analgesic efficacy was measured by hemodynamic parameters (HR, MAP). They concluded that suppression of sympathetic response to laryngoscopy and intubation was better with butorphanol than fentanyl. The emergence time, recovery time and post-operative sedation was less in the fentanyl group while post-operative analgesia was more in the butorphanol group. There was no evidence of nausea and vomiting in both groups. They concluded that butorphanol provides better analgesia with total intravenous anaesthesia as compared to fentanyl.

LD Mishra, N Rajkumar, et al (2009)[11] published a study 'A Comparative Study of propofol and isoflurane anaesthesia; using butorphanol in neurosurgery'. Sixty craniotomy patients randomly divided into two groups of 30 each were included in this study. Group A patients were induced and maintained with Propofol. Group B patients were induced with thiopentone and maintained with Isoflurane. All patients were administered 30µg/kg butorphanol intravenously 10 minutes before induction of anaesthesia, followed by slow injection of 30µg/kg Midazolam. All were assessed for sedation, respiratory insufficiency, postoperative nausea and vomiting and other side effects in the recovery room. They found fall in HR after butorphanol and was maintained in the post induction/intubation period and throughout the intraoperative period in Group A, unlike Group B patients in whom it rise significantly following intubation. Butorphanol was found to be a safe intraoperative analgesic in neurosurgical patients. In addition, it was associated with statistically better hemodynamic and earlier recovery when used with propofol as compared to thiopentone - isoflurane anaesthesia.

Priti M Chawda, Mayuresh K Pareek, et al (2010)[16], noted the effect of Nalbuphine on Haemodynamic Response to Orotracheal Intubation. Study was undertaken on 60 patients posted for elective laparoscopy surgery to receive either saline (group I, control group, n=30) or Nalbuphine 0.2mg/kg (group II, study group, n=30) as a bolus dose, 5 minutes before laryngoscopy. Heart rate and mean arterial pressure were taken 3 minute after study drug, just after intubation, then after every minute till 5 min and after 10 min of intubation. Twenty percent rise in heart rate and mean arterial pressure was considered as significant. There was significant rise in heart rate (20.4%) in group I after intubation at compared with baseline as compared to group II (16.66%). Mean arterial pressure showed rise of 12.35% in group I and 4.39% in group II after intubation but it was not statistically significant. They concluded that Nalbuphine 0.2 mg/kg prevented a marked rise in heart rate and mean arterial pressure associated with laryngoscopy and orotracheal intubation.

MATERIAL AND METHODS

For this study approval from ethical committee of Govt. Medical College and allied hospital, Kota was obtained and informed consent was obtained from all the patients. This study was conducted on sixty adult patients of either sex belonging to ASA grade I/II with Glasgow Coma Scale Score of 13 or more, who were operated for craniotomy under balanced general anaesthesia.

Exclusion criteria

The following patients were excluded:

1. Patient with serious, potentially life-threatening diseases, who were not optimally managed,
2. Patient with obvious anatomical contraindication to tracheal intubation (Mallampati scoring III & IV), previous history of difficult intubation, and those with irritable upper airway,
3. Patient having disorder of neuromuscular junction and myopathies,
4. Patient with systemic disorders like hepatic or renal insufficiency,
5. Patient with history of allergy to any drug used in this study,
6. Patient in whom extubation was delayed or elective ventilation needed were also excluded from the study.
7. Patient who had excessive intraoperative blood loss resulting in sudden change in haemodynamics.

Detailed preanaesthetic evaluation and routine investigations were carried out in all patients which included haemogram, Bleeding time (BT), clotting time (CT), blood sugar, serum urea, serum creatinine, routine urine examination, chest X-ray (PA view) and ECG.

All the patients were kept nil by mouth after 12 P.M. in the previous night of surgery. On arrival in Operation Theater, an intravenous cannulation was secured and baseline heart rate (HR), blood pressure (BP) and oxygen saturation (SpO_2) were recorded. All patients were premedicated with midazolam 0.03 mg/kg and glycopyrrolate 0.004mg/kg. The patients were randomly assigned to one of two groups with 30 patients in each category. Then group A patients received Butorphanol 2mg and group B patients received Nalbuphine 10mg with premedication. Each drug was preset to ten ml of the total volume mixed with normal saline and the syringes were labelled "study drug" by a fellow anaesthetist. The calculated dose of the study drug was given by fellow anaesthesiologist ten minute before induction. The name of study drug was revealed by fellow anaesthetist in postoperative period after completion of study period ie. 5 hour. After preoxygenation induction of anaesthesia was done with inj. propofol 2mg/kg IV followed by inj. succinylcholine 2mg/kg IV and IPPV with 100% oxygen. Then intubation with proper size of flexometallic cuffed endotracheal tube was done after complete relaxation.

Pulse rate, blood pressure (systolic and diastolic) and oxygen saturation were noted before premedication and at 3, 5 and 10 minute after premedication and study drug administration and after induction and intubation.

Maintenance of anaesthesia was done with isoflurane 1-2% in 100% oxygen. The end tidal concentration of isoflurane was titrated to keep the hemodynamic parameters near to base line values. Intermittent doses of vecuronium bromide were given in both the groups as and when required. Ventilation was adjusted to maintain end tidal carbon dioxide ($EtCO_2$) in the range of 30-35 mmHg in both the groups. The anaesthetic agent isoflurane was stopped after skull pin site closure in all patients. All the patients were monitored throughout the operation.

Pulse rate, blood pressure (systolic and diastolic) and oxygen saturation were recorded every 5 minute for initial 15 min., then every 15 min. till 90minutes then every half hourly during operation and then postoperative period till demand of postoperative analgesic dose.

Reversal was done after completion of surgical procedure. Patients were given inj. neostigmine 0.05 mg/kg IV with inj. 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 anaesthetic agent, extubation and recovery of consciousness were recorded.

In the recovery room the patients were assessed for Ramsay sedation score, postoperative nausea and vomiting (PONV) and duration of analgesia (time interval between analgesic administrations to the time when the patient complained of pain in recovery room) were recorded.

We used Ramsay sedation score for the assessment of sedation (Score1= Anxious, agitated, non-cooperative; Score 2= Cooperative, oriented, tranquill; 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; Score 6= No response to stimuli)[22].

Ramsay sedation score were observed every 15 minutes interval until the patient reached the sedation score of 2, which was considered to be the acceptable level of sedation as patients at this score were cooperative and tranquil[22]. Data was presented as mean ± standard deviation (SD). Data were analysed by unpaired t test for statistical analysis and $p<0.05$ were considered as statistically significant.

RESULTS

Both groups were comparable with respect to gender, age, weight, and duration of anaesthesia as shown in Table 1.

Table 1. Demographic Data

Variable	Group A N=30	Group B N=30
Age (yrs), mean (±SD)	35.27 ±11.77	34.8 ±11.9
Gender (M/F)	21/9	19/11
Weight mean (kgs) (±SD)	64.63 ±8.86	64.33 ±10.0

Table 2, 3 and 4 exhibits pulse rate, systolic and diastolic blood pressure at different intervals. Baseline mean pulse rate and blood pressure (Systolic and Diastolic) was almost similar in both groups. The study showed there was no significant difference between both groups regarding hemodynamic stability. There was a insignificant fall in pulse rate, systolic and diastolic blood pressure following midazolam and study drug (butorphanol or nalbuphine) administration in both groups. The fall in heart rate, systolic and diastolic blood pressure was maintained in the post induction/intubation period and throughout the maintenance of anaesthesia in both groups.

Table 2. Heart Rate (Beat/min.) mean±S.D

	Group A	Group B	P=Value
Baseline	83.00 ±6.76	80.90 ±7.96	0.28
After Premedication	81.03 ±6.40	79.77 ±7.81	0.49
Post Induction	73.23 ±6.17	71.03 ±6.15	0.17
Post Intubation	78.57 ±7.04	78.77 ±7.95	0.92
Post Extubation	87.67 ±7.29	85.8 ±7.16	0.32
Post Recovery of Consciousness	83.03 ±7.36	82.00 ±6.87	0.58

Table 3. Systolic Blood Pressure (mmHg) mean±S.D

	Group A	Group B	P=Value
Baseline	124.70 ±7.29	126.0 ±6.27	0.28
After Premedication	122.67 ±6.63	124.43 ±5.68	0.49
Post Induction	114.23 ±5.26	115.80 ±5.14	0.25
Post Intubation	120.07 ±6.03	119.70 ±5.43	0.81
Post Extubation	128.80 ±5.89	128.27 ±5.02	0.71
Post Recovery of Consciousness	123.67 ±5.03	122.47 ±4.72	0.34

Table 4. Diastolic Blood Pressure (mmHg) mean±S.D

	Group A	Group B	P=Value
Baseline	81.60 ±7.03	82.80 ±6.76	0.50
After Premedication	80.30 ±6.54	81.53 ±6.51	0.47
Post Induction	72.93 ±6.11	74.83 ±5.87	0.22
Post Intubation	76.60 ±6.15	78.57 ±6.46	0.23
Post Extubation	85.67 ±5.89	87.43 ±5.70	0.24
Post Recovery of Consciousness	82.83 ±5.00	83.60 ±5.67	0.58

Table 5. Exhibits Mean Values of Duration of Anaesthesia, Extubation Time, Recovery of Conciousness and Duration of Analgesia

	Group A	Group B	P=Value
Duration of anaesthesia	161.2 ±61.81	165.57 ±66.50	0.79
Extubation time	16.73 ±4.29	14.77 ±3.93	0.07
Recovery of Consciousness	19.63 ±5.37	17.27 ±4.35	0.07
Duration of analgesia	253.33 ±34.97	327.33 ±42.99	<0.05

Duration of analgesia was statistically significantly different when group A and group B were compared ($p<0.05$).

DISCUSSION

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. 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 patients comfort and safety. Narcotic analgesics are used preoperatively because they allay 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. Disadvantages of these drugs include prolonged awakening, nausea and/ or vomiting, respiratory depression, and a high addiction potential. A drug which would retain the benefits of existing narcotics but eliminate their disadvantages would be advantageous[8]. The use of intravenous narcotics in balanced anaesthesia is a well-recognized technique in anaesthesia[5]. Pure opioid agonists like morphine and pethidine carry the risk of dose related respiratory and cardiovascular depression, nausea, vomiting and addiction potential. Nalbuphine and Butorphanol are agonist - antagonist opioid analgesic with cardiovascular stability and lesser potential for respiratory depression[22].

There is no report on the comparison of Butorphanol and Nalbuphine in neurosurgical patients. Priti M et al.[16], observed that nalbuphine 0.2mg kg^{-1} administered 5 minutes before laryngoscopy prevents rise in HR and MAP following laryngoscopy and endotracheal intubation.

Pandit and Kothary [15], observed that thiopentone/ butorphanol induction provides statistically insignificant haemodynamic responses to tracheal intubation in laparoscopic outpatient procedures. Anil Agarwal et al.[1], observed the pain relieving property of butorphanol premedication given prior to intravenous propofol. This pain relieving property has a favourable effect prior to neurosurgical procedures by lowering patient's anxiety and the accompanying hemodynamic alteration. Mishra LD et al.[11], reported that butorphanol 30 µg /kg blunt the haemodynamic response when used with propofol, which is an advantageous factor in procedures related to neurosurgery.

F. N. Minai et al.[13], 2003 concluded that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater haemodynamic stability, as a component of balanced anaesthesia.

According to Richard L. McCammon[17] et al. in 1984 butorphanol (2 mg) or nalbuphine (10 mg) was considered equianalgesic to fentanyl (100µg) or morphine (10 mg). In healthy volunteers, butorphanol (0.03 or 0.06 mg/kg IV) produces no or minimal cardiovascular changes[10]. Nalbuphine (0.2mg kg^{-1}) administered 5 minutes before laryngoscopy prevents rise in heart rate and mean arterial pressure following laryngoscopy and endotracheal intubation[8].

Intraoperative Changes in Vital Parameters

Our results showed there was no significant difference between both groups regarding hemodynamic stability. There was a insignificant fall in pulse rate, systolic and diastolic blood pressure following premedication with midazolam and study drug (butorphanol or nalbuphine) and propofol induction in both groups. The fall in heart rate, systolic and diastolic blood pressure was maintained in the post induction/intubation period and throughout the maintenance of anaesthesia in both groups. Sympathetic response of intubation was supressed by both the drugs equally. As glycopyrrolate was added to the premedication which may cause tachycardia the combination of Propofol with Nalbuphine

/Butorphanol was still able to decrease the pulse rate, though minimally. This decline (attenuates the haemodynamic and somatic response to laryngoscopy and orotracheal intubation) was attributed to three reasons: sedation and anxiolysis caused by Midazolam and secondly sedation and analgesic effects of nalbuphine or butorphanol and lastly sedation and direct myocardial depressant action of propofol.

Similar results with respect to butorphanol were noted by L.D. Mishra et al[11]. Likewise Del pizzo[3,19] compared intramuscular Butorphanol 2 or 4 mg and Pethidine 80 mg used as a preanaesthetic medication. In this double blind study comparison of intramuscular Butorphanol and Pethidine showed no significant changes in blood pressure, heart rate, respiration intraoperatively and postoperatively as well. The study by Foldes et al[7] also showed no statistically significant Haemodynamic changes in 10 healthy volunteers receiving 0.03 or 0.06 mg/kg Butorphanol intravenously. R.K.Verma. et al[22] found that suppression of sympathetic response to laryngoscopy and intubation was better with Butorphanol than fentanyl.

F. N. Minai et al[13] compared morphine and nalbuphine for intraoperative and postoperative analgesia. They found that 0.2 mg/kg dose of nalbuphine proved to be hemodynamically more stable compared to 0.1mg/kg of morphine. The haemodynamic response to intubation and skin incision was lower in the nalbuphine group.

Priti M Chawda et al[16] found that Nalbuphine 3-5 minutes before laryngoscopy in dose of 0.2mg kg^{-1} prevented haemodynamic response associated with laryngoscopy and tracheal intubation.

Billard et al[2] reported a significant increase in mean blood pressure (mean 50 mmHg, $p<0.05$) following intubation and that the haemodynamic response to intubation was decreased by the administration of fentanyl in a dose dependent manner. Our observations are similar to the study of Billard et al, despite the fentanyl being replaced by Butorphanol or Nalbuphine in our study.

Van Hamelrijck et al[21], studied on craniotomy patients. In 20 patients, anaesthesia was induced with fentanyl and thiopental sodium and maintained with fentanyl, isoflurane, nitrous oxide (N2O), and thiopental sodium infusion. Twenty patients were anesthetized with propofol loading infusion followed by a maintenance infusion at a fixed rate. In addition, alfentanil was administered as a loading bolus, followed by a variable-rate infusion, with additional doses as necessary to maintain hemodynamic stability. They observed that the decrease in MABP after induction with thiopentone followed by a significant increase in MABP and HR during intubation. Conversely the HR and MABP did not change during propofol loading infusion.

In our study no rise of pulse rate from baseline may be because use of propofol instead of thiopentone. Likewise Grounds et al[9] also found no change in heart rate following injection of propofol whereas there was tendency to initial tachycardia following thiopentone. It is a well-known fact that propofol causes significant myocardial depression and fall in MAP. When propofol combined with nalbuphine or Butorphanol, this fall was greater and both the combinations were effective to suppress the intubation response. Thus we may say that butorphanol and nalbuphine can also blunt the haemodynamic response when used with propofol, an advantageous factor in procedures related to neurosurgery.

Deep plane of anaesthesia with veccuronium and isoflurane was contributing factors. Towards the end of anaesthesia in both groups pulse and arterial blood pressure were gradually increased. This increased pulse and arterial blood pressure may be due to lighter plane of anaesthesia as the anaesthetic agent was discontinued after skull pin site closure and patients started regaining consciousness.

Postoperative Changes

Duration of analgesia in Group A (butorphanol) and Group B (nalbuphine) was 253.33±34.97 and 327.33±42.99 min. respectively. The duration of anaesthesia were statistically insignificant ($p>0.05$) but duration of analgesia were statistically significant ($p<0.05$) when both groups were compared. Del pizzo[3] found the duration of analgesia provided by intravenous butorphanol to be about 2 hour (0.5 mg dose) or 2-4 hours (1-2 mg dose). F. N. Minai et al[13] found the duration of analgesia provided by intravenous Nalbuphine about 5.8hr. Our results are similar to studies of Del pizzo[3] and F. N. Minai et al[13].

Postoperative Recovery

The mean Ramsay sedation score was comparable in both groups upto 30 min after extubation. The mean Ramsay sedation score at 45 minutes after extubation in group A was 2.57$\pm$0.57 whereas in group B it was 2.23$\pm$0.43, which is statistically different in both group ($P<0.05$). In group B (Butorphanol) mean Ramsay sedation score 2 was achieved at 75 min. after extubation, but in group A (Nalbuphine) sedation score 2 achieved at 90 min. after extubation. This show that sedation is unavoidable side effect of both Butorphanol and Nalbuphine when given in adequate doses but it is more with Butorphanol than Nalbuphine in this study. R.K.Verma. et al[22] also found that sedation is an unavoidable side effect of butorphanol when given in adequate doses. The incidence of PONV was nil among both study groups. Similar results with respect to butorphanol and nalbuphine were noted by R.K. Verma et al[22] and Priti M Chawda et al[16] respectively.

CONCLUSION

From this study and other mentioned previous studies, it can be concluded that premedication with butorphanol 2 mg) or nalbuphine 10mg administration 10minutes before induction with propofol 2mg/kg provides protective effect against haemodynamic responses after laryngoscopy and endotracheal intubation. In our study we found that if maintenance with 1-2% isoflurane in oxygen with single bolus dose of propofol has been found quite effective and showed better recovery in neurosurgical paients.

This randomized study of patients undergoing routine craniotomy showed no significant statistical differences in haemodynamic parameters between two groups who received analgesia by Butorphanol 2mg and Nalbuphine 10 mg for balanced anaesthesia. Both drugs appeared equally effective analgesic for this type of surgery.

We concluded that Butorphanol 2 mg or nalbuphine 10 mg with propofol 2mg/kg as anaesthesia induction agent and Isoflurane 1-2 % in oxygen for maintenance anaesthesia was found to be safe intraoperative analgesic with haemodynamic stability, as a component of balanced anaesthesia during craniotomy in adult patients of class I & II with glasgow coma scale of more than 13 or more. In patients receiving nalbuphine the mean Ramsay sedation

score 2 was achieved at 75 min. after extubation in comparison to Butorphanol i.e. at 90 min. Duration of analgesia was significantly longer in patients who received nalbuphine (5.5hr) than patients who received butorphanol (4hr).

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