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CLINICAL EFFICACY OF NALBUPHINE VERSUS BUTORPHANOL AS ANALGESIC ADJUVANT TO FENTANYL DURING SURGICAL PROCEDURES UNDER GENERAL ANESTHESIA- A DOUBLE BLIND COMPARATIVE STUDY

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ABSTRACT

Background- Noxious stimulation of surgery predictably leads to variable hemodynamic changes which can be modified by intraoperative opioid analgesia. The present study was aimed to comparatively evaluate the clinical efficacy of Nalbuphine with Butorphanol as analgesic adjuvant to fentanyl during surgical procedures under general anesthesia.

Method and Material- Sixty adult patients of ASA grade I and II of either sex, were randomized into two equal groups of 30 patients each. Patients of Group I N received Nalbuphine 10 mg and patients of Group II B received Butorphanol 2 mg intravenously, 15 min before induction of general anesthesia with propofol. The endotracheal intubation was facilitated by vecuronium bromide (0.1mg/kg) and anesthesia was maintained with isoflurane, nitrous oxide and oxygen. Changes in heart rate and systemic blood pressure were noted as primary variables and postoperative nausea, vomiting, respiratory depression, shivering or pruritus were noted as secondary outcomes.

Results- Patients of comparable demographic profile showed fall in heart rate and blood pressure after nalbuphine, but intraoperative hemodynamic changes were comparable between the groups. After extubation, patients of nalbuphine group were sedated but arousable while patients of butorphanol group were awake. No episode of nausea, vomiting, respiratory depression, shivering, pruritus or any other side effects occurred in any patient.

Conclusion- Nalbuphine and butorphanol, both could provide effective intraoperative analgesia as well as attenuated the hemodynamic response to surgical stress of surgical procedures.

KEYWORDS : Butorphanol; Nalbuphine; Hemodynamic Stress Response of Surgery;

INTRODUCTION

Surgical stress due to tissue injury, airway stimulation and pain initiate numerous physiological changes which may lead to variable hemodynamic changes of tachyarrhythmia and hypertension. [1] Manipulation of abdominal contents during surgical procedure also caused hemodynamic changes.

The magnitude of hemodynamic changes can be attenuated by using opioid analgesia, beta adrenergic blockers, alpha 2 adrenergic agonist, vasodilators, and by increasing the depth of anesthesia but with their inherent side effects such as respiratory depression, histamine release and gastrointestinal effects.

Opioid analgesics act presynaptic and post synaptic sites in the central nervous system to activate the pain modulating systems. Opioid receptors also exist on the peripheral ends of primary afferent neurons, where their activation, decrease neurotransmission and inhibit the release of excitatory neurotransmitters. The major pharmacodynamics differences between the various opioids are their potency and rate of equilibrium between the plasma and the site of drug action. [2]

Fentanyl is synthetic opioid analgesic with activity as μ receptor agonist and is significantly more potent than commonly used opioids. The wide margin of safety, relatively short duration of action and ability to provide cardiovascular stability with minimal respiratory depression, has made it drug of choice.

Nalbuphine and butorphanol are synthetic opioid agonist-antagonist analgesics. They are principally κ receptors agonist and μ receptor antagonist and exert their action by opening the K^+ channels and reducing the Ca^{++} influx, resulting in inhibition of transmitter release, hence blocking nociceptive impulses from the surgical site. Respiratory depression is less with kappa receptors agonist, although dysphoria and diuresis may accompany. [3,4]

The advantages of opioid agonist-antagonists are their ability to produce analgesia with only partial respiratory depression with ceiling effect and low potential to produce physical dependence. [5]

The objective of this prospective double blind randomized study was to comparatively evaluate the clinical efficacy of nalbuphine with butorphanol as analgesic adjuvant to fentanyl during surgical procedures conducted under general anesthesia.

MATERIALS AND METHODS

The study protocol was approved by Institutional Ethical Committee and informed consent was obtained from each patient. This prospective double blind randomized study was conducted on 60 adult patients of American Society of Anaesthesiologist (ASA) physical status I and II aged 21 to 56 years of either gender, who were scheduled for elective surgical procedures under general anaesthesia.

Patients with history of cardiac dysfunction or respiratory difficulty, hepatic or renal insufficiency, endocrine or metabolic disorder and morbid obesity, were excluded from the study. Patients taking any medication like antihypertensive or analgesics, which could modify the stress response of surgery and anesthesia, were also excluded from the study. None of the patients have previous experience of anesthesia.

Sixty enrolled patients were divided into two equal groups of 30 patients each according to a computer generated random number table. Patients of Group I (N) were given Nalbuphine 10 mg and patients of Group II (B) were given Butorphanol 2 mg intravenously, 15 min before induction of general anesthesia. Study medication was prepared by an anaesthesiologist by dissolving the study drugs in 10 ml of normal saline. The randomization schedule was not known to him and was not further involved for data collection, to keep the blindness of study.

Anesthetic Technique

All patients were given tablet alprazolam 0.25 mg and tablet ranitidine 150 mg orally prior night before surgery and their 6 hours fasting was ensured prior to surgery.

On the day of surgery, they received inj. glycopyrrolate 0.2 mg intramuscularly, 30 minutes prior to induction of anesthesia. On arrival to operation theatre, Multipara monitor was attached and baseline vital parameters of heart rate, systemic blood pressure, electrocardiogram and peripheral oxygen saturation (SpO_2) were recorded and an intravenous was line secured to start the lactate Ringer solution at rate of 4-6 ml/kg/h.

The patients of Group I (N) were given nalbuphine 10 mg and patients of Group II (B) were given butorphanol 2 mg intravenously, 15 minutes before induction of anesthesia. They were premedicated with ondansetron 4 mg, midazolam 2 mg and fentanyl 2 µg/kg, intravenously.

After 3 mi of preoxygenation, anesthesia was induced with propofol (2 mg/kg), till loss of verbal command. The laryngoscopy and intubation was facilitated with vecuronium bromide (0.1mg kg^{-1}) and anesthesia was maintained with isoflurane, 60% nitrous oxide and 40% oxygen. The patients were mechanically ventilated to maintain the normocapnia ($EtCO_2$ between 35-40 mm of Hg) by adjusting tidal volume and ventilatory frequency. The degree of muscle relaxation was maintained with supplemental doses of vecuronium bromide.

The patients were assessed for any changes in heart rate, blood pressure, and peripheral oxygen saturation along with analysis of electrocardiogram (ECG) for any change in rhythm and ST segment. These parameters were recorded at baseline, before and after induction, immediately after intubation and then at 5 min interval during intraoperative period till end of surgery and post extubation. The hemodynamic changes observed as abnormal finding during the study were defined as hypotension when systolic blood pressure was less than 20% of baseline value or less than 90 mm Hg, whichever was lower and hypertension was defined when systolic blood pressure was more than 20% of baseline value or more than 140 mm Hg whichever was higher. Tachycardia was defined as heart rate more than 100 beats/minute and bradycardia was defined as heart rate less than 60 beats/minute. Intraoperatively, any episode of hypotension, hypertension, bradycardia, or tachyarrhythmia, was managed by adjusting the dial concentration of isoflurane and rate of lactate Ringer solution. Record of each such patient was kept.

At the end of surgery, isoflurane was discontinued and residual neuromuscular blockade was antagonized with appropriate doses of neostigmine (0.05mg/kg) and glycopyrrolate (0.01 mg/kg). Patients were extubated after achieving signs of adequate reversal and he could able to obey simple verbal commands.

Patients were transferred to post anaesthesia care unit and monitored for any hemodynamic changes, respiratory depression, shivering, pruritus, or postoperative nausea and vomiting and treated accordingly.

Study Population Size and Statistical Analysis

The sample size was decided in consultation with statistician and was based on initial pilot observations which suggested that approximately 27 or 28 patients should be included in each group to ensure the power of study 80% and alpha error of 0.05 with confidence limit of 95% for detecting reduction by at least 20% in enhanced hemodynamic changes. Assuming a 5% drop out rate, the final sample size was set at 60 patients for better validation of results.

The data obtained in the study are presented in tabulated manner and variables are expressed as mean ± standard deviation (SD), considering the later as the best predictor for statistical analysis. The results were analysed using Stat Graphic Centurion for windows, (Stat point technologies INC, Warrenton, Virginia). The parameters of both group were compared using one way analysis of variance (ANOVA), Chi square test and unpaired T test. A p value of less than 0.05 was considered to indicate as statistical significance.

RESULTS

The present study compared the clinical efficacy of intravenous nalbuphine with butorphanol as analgesic adjuvant to fentanyl during surgical procedures conducted under general anesthesia on 60 adult patients of both genders. There was no protocol deviation and data of all patients were included for statistical analysis.

The demographic profile of age, weight, body mass index, gender ratio and ASA physical status were comparable between the groups. [Table 1]

Hemodynamic Changes

The hemodynamic parameters of heart rate and systemic blood pressure were monitored intra-operatively from induction till extubation and thereafter postoperatively.

The base line, the mean heart rate was comparable between the groups (85.3±8.6 vs 87.2 ± 7.2 beats/min). Patients of nalbuphine group showed fall in mean heart rate from base line till 10 minutes after induction with statistically significant difference between the groups. The difference in mean heart rate was maximal at 5 minutes after intubation. The mean heart rate in patients of nalbuphine group remained lower throughout the intraoperative period, when compared to patients of butorphanol group but with no statistically significant difference. [Table-2]

The mean systolic blood pressure at base line was comparable between the groups (121.27± 6.78 vs 117.27±7.41 mm Hg) and was minimal at induction in patients of both groups. It remained lower in patients of nalbuphine group when compared to butorphanol group. The difference in mean systolic blood pressure decreased with time from induction till completion of surgery and difference between the groups was not significantly significant. [Table-3]

The postoperative hemodynamic parameters did not show any changes. No patient in either group had any episode of hypotension, pruritus, nausea and vomiting, shivering or respiratory depression in the postoperative period. No other complications related to study drug or anesthetic technique occurred during the study period.

DISCUSSION

Surgical stress stimulation, endotracheal intubation and pain initiate sympathetic over activity, leading to increased blood pressure, heart rate, occasional dysrhythmias and plasma catecholamine concentration. Nociceptive pathways and humoral mediators, originating from the surgical site do enhance the adrenergic responses. [1, 2] Although these hemodynamic changes are transient but are detrimental in patients with pre-exiting myocardial or cerebral insufficiency. These adverse hemodynamic responses could be attenuated by using opioid analgesics, alpha 2-adrenergic agonist, beta adrenergic blocking agents and vasodilators but with variable results.

Opioid receptors are located in areas of the brain and spinal cord and are involved with pain perception, integration of pain impulses and responses to pain. These receptors also exist on the peripheral ends of primary afferent neurons, resulting in activation of pain modulating (antinociceptive) systems. The opioid receptors activation decreases the neurotransmission, mainly by presynaptic inhibition of neurotransmitter release, although postsynaptic inhibition of evoked activity may also follow. [6]Administration of an opioid before surgical stimulation may decrease the subsequent amount of opioid required for postoperative analgesia.

The significance of study lies in the fact to select the better drug as an analgesic adjuvant to fentanyl for surgical procedures which could attenuate the hemodynamic pressor response of stress, as both, nalbuphine and butorphanol are mixed agonist antagonist opioid.

Nalbuphine is primary κ agonist and μ antagonist and its analgesic potency is equal to morphine. Naloxone can reverse its agonist effects. Nalbuphine does not increase systemic blood pressure and heart rate, thus may be useful in providing sedation and analgesia for cardiac patients.[3,7] Butorphanol has low affinity for μ receptors to produce antagonism and moderate affinity for κ receptors to produce analgesia and antishivering effects. Analgesic doses of butorphanol increase systemic blood pressure and cardiac output. Common side effects of butorphanol include sedation, nausea and diaphoresis. [4]

A single dose of fentanyl administered intravenously, has more rapid onset but shorter duration of action due to redistribution to inactive tissues. If given 5 min before induction of anesthesia, it decreases the subsequent doses of isoflurane to block the sympathetic responses to surgical stimulation.

The precise mechanism that leads to hemodynamic changes involve intense sympathetic discharge and release of catecholamine. In the present study, after administration of fentanyl with either nalbuphine or butorphanol, there was fall in mean heart rate and systolic blood pressure in patients of both groups with no statistically significant difference between the groups. After induction, the difference in heart rate changes was statistically significant between the groups, but decrease in systolic blood pressure was more evident in patients of nalbuphine group.

The heart rate was increased during laryngoscopy and intubation and was more marked in patients of butorphanol group when compared to patients of nalbuphine group. The difference between the groups was statistically significant till 5 minutes after intubation. It was evident from the present study that nalbuphine was able to attenuate hemodynamic response of laryngoscopy and intubation. In patients of nalbuphine group, the initial fall in all the hemodynamic parameters was due to its strong and predominant kappa agonistic effects. Increase in hemodynamic parameters after endotracheal intubation was due to sympatho-adrenal stimulation of pharyngeal structures during direct laryngoscopy. Ahsan-ul-Hag et al also reported an increase in heart rate of 15.5% and mean arterial pressure of 10.5% with nalbuphine immediately after intubation. Their observations are in concurrence of the present study. [8]

Peak effects of nalbuphine are seen approximately 20 min after its administration which could be seen in present study as the heart rate and blood pressure started return towards baseline approximately 5 min after intubation, whereas in butorphanol group the hemodynamic pressor response was sustained up to 15 min post laryngoscopy.

Various studies have also concluded that fentanyl and nalbuphine are effective in keeping the patients hemodynamically stable and the results of present study are in accordance with previous clinical studies. [9]

Chestnut et al compared the effects of nalbuphine, pethidine and placebo. They noticed the tremendous control of hemodynamic response during gynaecological surgery in nalbuphine and pethidine group, but noticed nausea and vomiting at the end of surgery which was more evident in patients of pethidine group. [10] Kothari and Sharma also used nalbuphine and noticed effective reduction in heart rate and mean arterial pressure as compared to pentazocine. [11]The present study also supports their results.

In the present study, intravenous nalbuphine or butorphanol before induction of anesthesia, has modified the hemodynamic pressor responses of laryngoscopy and surgical stimulation but could not totally abolish them. The variations of blood pressure and heart rate never exceeded more than 15% of baseline which could be attributed to their analgesic potency.

Hypotension and bradycardia was not observed in any patient during the study period, hence intravenous atropine or vasopressor was not used. This may be because of adequate pre-anesthetic plasma volume expansion and intramuscular glycopyrrolate premedication.

Chug et al observed that pure agonists can cause complications such as respiratory depression which can be dangerous in the recovery room. [12] On the other hand, nalbuphine and butorphanol are agonist-antagonist opioid and cause less respiratory depression by acting the supraspinal and spinal kappa receptors. [13] Hence, in the present study, no postoperative respiratory depression was observed in any patient. Lower incidences of pruritus, respiratory depression and postoperative nausea and vomiting (PONV) with nalbuphine when compared to morphine, was observed by many researchers. [14,15]

CONCLUSION

Nalbuphine has more effectively attenuated the stress response of laryngoscopy and surgical stimulation when compared to butorphanol, but both drugs provided valuable intraoperative analgesia for major abdominal surgery performed under general anesthesia.

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this clinical study.

Table 1: Showing demographic profile

	Group I (N)	Group II (B)	P-value
Age (year)	43.74±10.2	45.36±9.2	0.79
Weight (Kg)	57.63±5.6	57.18±5.5	0.67
BMI (Kg/m2)	22.78 ±1.02	22.73 ±0.7	0.56
Gender (M/F)	24/6	25/5	0.78
ASA (I/II)	21/9	22/8	0.85

Table 2: Showing Changes in Mean Heart Rate (beats/min)

Time	Group I (N)	Group II (B)	P-value
Base line	85.3± 8.6	87.2 ±7.2	.067
Induction	72.27±5.41	76.67± 6.5	0.07
5min	77.80 ± 7.21	85.40± 6.8	<0.05*
15min	79.93±7.92	87.12 ± 6.02	<0.05*
30min	78.67±7.75	84.11± 7.9	0.10

45min	78.43±8.06	87.90± 7.48	0.125
60 min	81.43± 8.05	88.4± 7.81	0.067
90min	85.32± 6.19	91.80 ±5.74	0.076
Post extubation	87.47±8.35	93.7±3.81	0.063

Table 3: Changes in Systolic Blood Pressure

SBP	Group I (N)	Group II (B)	P-value
base line	121.27±6.78	117.27±7.41	0.067
Induction	109.27±6.741	116.40±5.89	<0.05*
5min	116.87±11.13	122.87±8.60	0.004*
15min	112.80±10.16	117.47±6.882	0.07
30min	110.67±7.77	112.87±5.251	0.089
45min	108.00±7.06	112.80±5.36	0.14
60 min	109.27±6.36	115.27±4.55	0.076
90min	115.71± 6.34	119.27±7.83	0.086
Post extubation	124.91±4.36	131.72±2.74	0.062

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