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EFFECT OF NALBUPHINE AND PENTAZOCINE ON ATTENUATION OF HEMODYNAMIC CHANGES DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

Anaesthesiology

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ABSTRACT

Background: Several drugs have been traditionally used to blunt the sympathetic response to direct laryngoscopic intubation. In this study we compared the effects of pentazocine and Nalbuphine along with a control on this pressor response to intubation. **Method:** Ninety patients under general anaesthesia were evaluated. They were randomly divided into three groups. Group N patients received 0.3 mg/kg of nalbuphine, group P received 0.5mg/kg of pentazocine while group C received 5ml of normal saline (control group) 5 min. prior to intubation intravenously. Heart rate, systolic blood pressure and diastolic blood pressure were recorded. **Results:** It was observed that, in group C, after laryngoscopy and intubation, there was rise in heart rate, systolic and diastolic blood pressure. These values were highest at 1 min post intubation and remained high thereafter also. In P group there was rise in all the parameters immediately after laryngoscopy and intubation which came to baseline at 10 min post intubation and were lesser as compared to control group. With nalbuphine, there was small rise in hemodynamics immediately after intubation which came to baseline at 5 min post intubation. There was statistically significant attenuation of pressor response than control and pentazocine. **Conclusion:** Thus, it was concluded that Nalbupine was a better drug in obtunding the pressor response as compared to pentazocine.

KEYWORDS

Nalbuphine, Pentazocine, Intubation, Pressor response, Laryngoscopy

INTRODUCTION

Laryngoscopy and endotracheal intubation are an integral part of general anaesthesia practice. In 1940, Reid and Brace[1] first described that direct laryngoscopy and tracheal intubation during general anaesthesia gives rise to intense sympathetic response and increased catecholamine release. This, in turn, leads to tachycardia, hypertension, dysrythmias and even myocardial ischemia; this is known as pressor response to laryngoscopy and intubation. Organs involved in pressor response to laryngoscopy and endotracheal intubation are base of tongue, epiglottis, soft palate, pharynx, epipharyngeal region and larynx, which are extensively innervated by autonomic nervous system. Sympathetic supply is via superior cervical ganglion whereas parasympathetic supply is via the vagus nerve. Stimulation of above-mentioned areas particularly epipharyngeal region (most sensitive area)[2] leads to coughing, laryngospasm, bronchospasm, vomiting, and pulmonary aspiration, increase in intracranial as well as intraocular pressure and cardiovascular changes like tachycardia, systemic arterial hypertension, cardiac arrhythmias including asystole and bradycardia in children[3,4,5].

These effects may occur even in routine uneventful normal induction; but they are further aggravated by light planes of anaesthesia, hypoxia, hypercarbia, anxiety and also in poorly controlled hypertensives. These adverse cardiovascular effects are generally well tolerated in normal individuals. However, in patients with preexisting hemodynamic compromise like coronary artery disease, poor myocardial function and in open eye injury, increased intracranial pressure etc., these changes are of grave significance and may have fatal consequences[6]. Hence various methods and drugs have been tried to reduce this response[7-9]. Various opioids have also been used to attenuate pressor response such as fentanyl, alfentanil etc[10,11].

Nalbuphine is a semi-synthetic agonist-antagonist opioid analgesic of the phenanthrene series. It is indicated for relief of moderate to severe pain. It can also be used as a supplement to balance anaesthesia, for preoperative and postoperative analgesia. Pentazocine is a synthetically prepared agonists-antagonists opioid of benzomorphan group. It is also commonly used to treat mild to moderately severe types of pain. It is cheap and easily available in India[12]. It is commonly used in most of the hospitals in our country. But no study has been done to evaluate its effect to attenuate haemodynamic response to laryngoscopy and intubation. Hence the present study was undertaken to evaluate the effectiveness of intravenous nalbuphine and intravenous pentazocine to attenuate haemodynamic response associated with laryngoscopy and endotracheal intubation and its effects were compared with the control group (patients not receiving any of these drugs.)

MATERIAL AND METHODS

A prospective, randomized, placebo controlled, double blind clinical study was conducted after approval from the institutional ethical committee. The study was carried out on 90 patients to evaluate the effect of intravenous nalbuphine and pentazocine on haemodynamic response to direct laryngoscopy and tracheal intubation and compare their effects.

Sample Size Calculation:

Taking into consideration the mean MAP (mean ± SD) after 3 min of study drug administration as the main outcome of interest and from the previous study in which the mean value being 93.5±8.07 in the nalbuphine group and 97.9±8.20 in the pentazocine group (difference of 4.4).[13] The simplest formula for a continuous outcome and equal sample sizes in study groups, assuming: $\alpha = 0.05$ and power of study = 0.80; ($\beta = 0.20$, therefore $1-\beta=0.8$).

$$n = \frac{2[(a+b)^2\sigma^2]}{(\mu_1 - \mu_2)^2}$$

n = the sample size in each of the groups
μ1 = population mean in treatment Group 1
μ2 = population mean in treatment Group 2
μ1 − μ2 = the difference of means
σ2 = population variance (SD) = 6
a = conventional multiplier for alpha = 0.05
b = conventional multiplier for power= 0.80
When the significance level alpha is chosen at 0.05, then value of a= 1.96. Similarly, when beta is chosen at 0.20, the value of b = 0.842.

$n = 2 \times ([1.96 + 0.842]^2 \times 6^2)/4.4^2$
$n = 2 \times 7.851 \times 36 / 19.36$
$n = 565.272 / 19.36$
$n = 29.19 \sim 30$
Sample size round figure into 30 patients in each group. Hence a total of 90 cases were selected for the study meeting the following inclusion criteria:

Inclusion criteria:

1. Patients between 18-60 years of age.
2. Patients with ASA grade I-II of either sex.
3. Patients undergoing elective surgery requiring general anaesthesia with endotracheal intubation.

4. MPC grade I and II.

Exclusion criteria:

1. Patient with known history of hypersensitivity to the drugs used.
2. History of hypertension or ischemic heart disease.
3. History of chronic obstructive lung diseases, respiratory insufficiency
4. Anticipated difficult intubation.
5. Acute renal, liver insufficiency.
6. Patient refusal to participate.
7. Increased intracranial pressure.
8. ASA grade III or more.
9. Lactating mothers and pregnancy.
10. Bucking and coughing after intubation.
11. More than one attempt at intubation.

Patients scheduled for elective surgeries were thoroughly evaluated and assessed preoperatively. All patients were adequately investigated. After patients were found to be suitable for inclusion in the study, they were explained about the nature of study in their language and informed consent was taken for participation in the study. Patients were randomly divided into three groups of 30 patients each. Group N patients received 0.3 mg/kg of nalbuphine, and group P received 0.5mg/kg of pentazocine while group C received 5ml of normal saline (control group) 5 min. prior to intubation intravenously.

All the patients underwent the same anaesthetic technique as below. Preoperatively, patients were kept fasting for 8 hrs. Inj. glycopyrrolate bromide 4mcg/kg was given intramuscularly 30 minutes prior to surgery. All the necessary equipments and drugs including the emergency resuscitation were checked and kept ready. Cardioscope, Pulseoxymeter, Non-invasive blood pressure were monitored.

After measuring the baseline preoperative parameters like heart rate and blood pressure, intravenous fluid infusion was started. All patients were given Inj.ondansetron 0.1mg/kg i.v. and Inj. midazolam 0.03 mg/kg i.v. as premedication. After 5 minutes nalbuphine or normal saline or pentazocine as per group was injected slowly in double blind fashion. The patients were pre-oxygenated with 100% oxygen with Bain's circuit. After 5 minutes, all patients were induced with intravenous 2.5% Thiopentone Sodium 5-7 mg/kg till loss of eyelash reflex. This was followed by Inj. Suxamethonium 1.5 mg/kg i.v. laryngoscopy and endotracheal intubation with proper sized cuffed endotracheal tube were carried out using Macintosh laryngoscopy blade by the same person each time. Patients requiring more than one attempt at intubation, desaturation, bucking, coughing etc., were excluded from the study. After intubation, anaesthesia was maintained with 50% Oxygen, 50% Nitrous oxide and Sevoflurane. Muscle relaxation was maintained with inj. atracurium. All the three groups were evaluated for complications like bradycardia, hypotension and any other side effects of both the study drugs.

The hemodynamic parameters included heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation (SpO_2%) and any changes in electrocardiogram were recorded before induction, after induction, at laryngoscopy and intubation and at 1, 3, 5, 10 minutes. Monitoring continued throughout the intraoperative period and post-operative period. Patients in the control group were given Inj. Fentanyl 2mcg/kg i.v. to ensure balanced anaesthesia.

ECG monitoring was done to note any cardiac irregularities and continued throughout the procedure. Observations were tabulated in the following manner, statistically analyzed and conclusions drawn.

Parameters	HR	Systolic BP	Diastolic BP	ECG changes	SPO2
Before IV induction					
After IV induction					
At intubation					
At 1 minute					
At 3 minutes					
At 5 minutes					
At 10 minutes					

Statistical Analysis

Mean and standard deviation for all values were calculated and compared within the group with the baseline values as well as intergroup comparison was done. One-way repeated measure ANOVA, Unpaired T test and Chi square test were used for statistical analysis. P value □ 0.05 was considered statistically significant. Statistical software STATA VERSION 20.0 was used for data analysis.

OBSERVATIONS AND RESULTS

This study evaluated 90 patients that were randomly divided into three groups-

Group C Control group
Group P Pentazocine group (0.5 mg/kg)
Group N Nalbuphine group (0.3 mg/kg)

There was no significant difference with respect to gender, age, and weight in between the three groups as shown in table 1.

Table 1: Demographic profile of the patients

Demographic data		Control	Pentazocine	Nalbuphine	P value
Age in years	Mean	36.50 ± 10.84	38.80 ± 11.09	38.33 ± 12.10	0.71
Weight (kgs)	Mean	52.27 ± 6.31	54.43 ± 11.98	54.20 ± 7.85	0.597
Gender	Male	16 (53.33%)	16 (53.33%)	15 (50.0%)	>0.05
	Female	14 (46.67%)	14 (46.67%)	15 (50.0%)	

By using ANOVA, it was observed that there was no significant difference between the groups before induction, after induction but there was significant difference at 0 min, 1st min, 3rd min, 5th min and 10th min. with respect to heart rate, (Table 2 and Chart 1)

Table 2: Comparison of mean heart rate in control, pentazocine and nalbuphine group

Mean Heart rate/min	Group			p-value
	Control	Pentazocine	Nalbuphine	
Before induction	80.36 ± 8.90	80.57 ± 10.59	78.16 ± 8.89	0.663N
After induction	81.70 ± 6.73	81.40 ± 8.90	78.30 ± 7.31	0.172N
at 0 min	99.53 ± 11.84	91.13 ± 10.06	85.83 ± 7.26	< 0.001S
at 1st min	109.83 ± 10.41	89.56 ± 8.90	84.37 ± 7.13	< 0.001S
at 3rd min	96.30 ± 6.72	84.80 ± 8.36	80.10 ± 6.61	< 0.001S
at 5th min	88.23 ± 7.56	81.80 ± 8.54	77.33 ± 6.69	< 0.001S
at 10th min	86.23 ± 8.29	79.40 ± 8.40	75.33 ± 6.84	< 0.001S

N: Not significant, S: significant

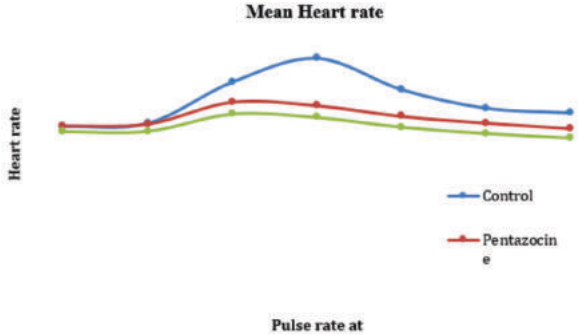

Chart 1: Comparison of mean heart rate in control, pentazocine and nalbuphine group.

Likewise, there was no statistically significant difference in SBP between the groups before induction and after induction. p-value < 0.05 therefore there was statistically significant difference between all the groups at 0 min ,1st min, 3rd min, 5th min and 10th min with respect to systolic blood pressure (SBP), (Table 3 and Chart 2).

Table 3: Comparison of systolic blood pressure (SBP) (mmHg) in control, pentazocine and nalbuphine group.

Mean Systolic blood pressure (mm of Hg)	Group			p-value
	Control	Pentazocin e	Nalbuphine	
Before induction	121.27 ± 8.50	122.63 ± 9.10	123.8 ± 11.35	0.602N

After induction	124.2 ± 9.23	123.03 ± 8.50	124.27 ± 7.10	0.812N
at 0 min	149.13 ± 11.10	138.53 ± 9.00	130.33 ± 8.80	< 0.001S
at 1st min	152.8 ± 7.96	139.63 ± 7.92	129.2 ± 10.02	< 0.001S
at 3rd min	139.93 ± 7.32	134.2 ± 8.70	128.93 ± 9.61	< 0.001S
at 5th min	133.53 ± 7.31	127.9 ± 9.36	123.2 ± 8.67	< 0.001S
at 10th min	128.3 ± 7.04	122.47 ± 9.10	119.83 ± 7.83	< 0.001S

N: Not significant, S: Significant.

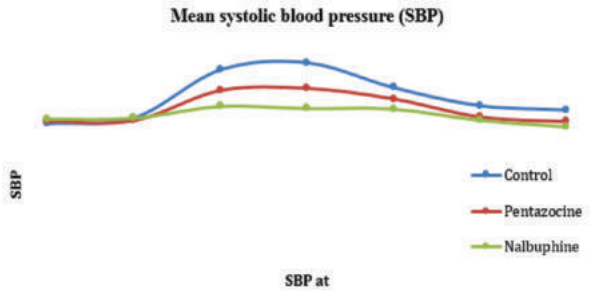

Chart 2: Comparison of systolic blood pressure (SBP) (mmHg) in control, pentazocine and nalbuphine group.

Similarly, there was no statistically significant difference between the groups before induction and after induction. But there was a statistically significant difference at 0 min, 1st min, 3rd min, 5th min and 10th min. with respect to diastolic blood pressure (DBP), (Table 4, Chart 3)

Table 4: Comparison of diatolic blood pressure (DBP) (mmHg) in control, pentazocine and nalbuphine group.

Mean diastolic blood pressure (mm of Hg)	Group			p-value
	Control	Pentazocine	Nalbuphine	
Before induction	74.6 ± 6.67	75.03 ± 7.12	75.46 ± 7.82	0.119N
After induction	75.67 ± 6.38	75.77 ± 6.96	75.13 ± 7.56	0.931N
at 0 min	92.93 ± 7.32	86.56 ± 7.27	81.30 ± 6.63	< 0.001S
at 1st min	99.66 ± 6.50	85.63 ± 6.50	81.57 ± 6.83	< 0.001S
at 3rd min	90.30 ± 6.61	82.43 ± 6.27	77.97 ± 7.27	< 0.001S
at 5th min	84.16 ± 6.16	78.83 ± 5.29	75.87 ± 7.79	< 0.001S
at 10th min	80.40 ± 6.47	74.83 ± 6.43	73.37 ± 8.28	< 0.001S

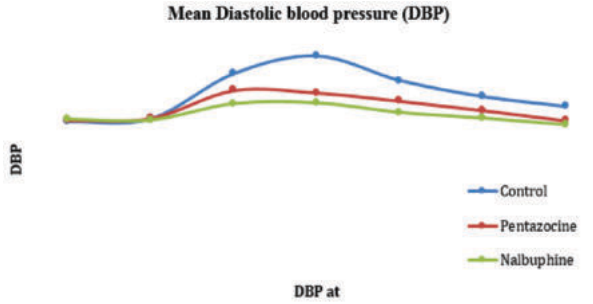

Chart 3: Comparison of diatolic blood pressure (DBP) (mmHg) in control, pentazocine and nalbuphine group.

ECG changes in three groups:
There were no significant ECG changes during laryngoscopy and intubation and till 10 min post intubation in all three groups.

Oxygen saturation changes in three groups:
There was no desaturation observed in all three groups during laryngoscopy and intubation and till 10 min post intubation. The saturation always remained between 97% to 100% in all three groups.

Adverse effects in study groups:
None of the patients had significant adverse effects like arrhythmias, ECG changes, desaturation, bradycardia etc. The other side effects like nausea and vomiting were not noted in our study groups.

DISCUSSION

Increase in heart rate and blood pressure has always been a matter of concern during laryngoscopy and intubation. Haemodynamic response to laryngoscopy and intubation has deleterious effects in patients suffering from hypertension, ischemic heart disease. Various techniques, equipment and drugs are used to attenuate the haemodynamic response of laryngoscopy and endotracheal intubation, but none is ideal. Most of the drugs used for this purpose are having their own side effects; some are costly and are not easily available[14].

Pentazocine and nalbuphine have many similarities in producing analgesia by action on κ receptor, but pentazocine is weaker μ receptor antagonist, or partial agonist as compared to nalbuphine which is strong μ receptor antagonist, due to this nalbuphine can reverse μ receptor associated all side effects such as respiratory depression, vomiting, and pruritis in contrast to pentazocine[15]. It has been found that nalbuphine is three times more potent than pentazocine on intravascular or intramuscular administration[16,17]. Therefore, the present study was planned to assess the efficacy of intravenous nalbuphine (0.3mg/kg) and intravenous pentazocine (0.5 mg/kg), in attenuating the cardiovascular responses to laryngoscopy and intubation.

In the present study, all the three groups were comparable and found no significant difference with respect to demographic data of patients (age, sex, and weight distribution).

In group C (control group), there was a cardiovascular stress response to intubation, as there was a rise in heart rate, SBP and DBP. These values were highest at 1 min. and remained high till 10 min post intubation which was statistically significant.

In group P (pentazocine group) patients, there was rise in heart rate, SBP and DBP at laryngoscopy and intubation till 3 min post intubation. The values started decreasing at 5 min post intubation and they were equal to baseline at 10 min post intubation. Thus, there was attenuation of haemodynamic response to laryngoscopy and intubation by pentazocine as compared to control group, which was statistically significant. However, this attenuation was still significantly lower as compared to the Nalbupine Group.

In group N (nalbuphine group), there was small rise in heart rate, SBP and DBP at laryngoscopy and intubation and 1 min. post intubation. These values started decreasing at 3 min post intubation and they were equal to baseline at 5 min post intubation, this could be attributed to strong and predominant k agonistic action[18]. Further could be attributed to effect of thiopentone sodium used as an induction agent for general anesthesia, a drug very well known for producing hypotension and associated reflex induced tachycardia[19,20]. In the current study, there was attenuation of pressor response by nalbuphine as compared to pentazocine and control groups, which was statistically significant. Similarly, Kothari D et al found a clinically significant rise in HR was observed with pentazocine (+24.11%) as compared to nalbuphine (+19.56%), although these values were statistically insignificant on intergroup comparison ($P > 0.05$). A statistically highly significant rise ($P < 0.01$) from basal mean values in all the three parameters of BP was observed immediately after intubation in both groups, but clinically this rise was more apparent with pentazocine[13].

Ahsan-ul-Haq et al noticed increases in heart rate just after induction which was significant i.e., more than 20% rise from baseline in placebo group. Our result can be compared to this study for heart rate increase. Our patients did exhibit a rise in heart rate in group N which was not significant. This difference can be explained by the adequate sedation effect of the premedication drug given 5 minutes before induction of anaesthesia. Rise in heart rate and MAP occurs due to elevations in plasma catecholamines levels which occurred markedly in group C while lesser increase in heart rate and MAP occurred following

intubation in patients receiving nalbuphine[21]. A study by Sadafule NN at al reported rise in heart rate, blood pressure after intubation in both groups but rise was more with Pentazocine as compared to Nalbuphine ($P < 0.05$)[12] as similar to present study. Pandèle et al also found significantly higher systolic blood pressure with pentazocine as compared to nalbuphine[22] same as to our study. However, Adachi et al reported that pentazocine 0.5 mg/kg failed to diminish the circulatory response to intubation[23]. On the other hand, Graham et al in their study found no significant changes in heart rate or blood pressure at induction and skin incision while using these two drugs[16].

Although Kay B et al compared the effects of three drugs on haemodynamic response to intubation. The pressor response to tracheal intubation which occurred after saline was reduced after nalbuphine, but tachycardia still occurred. In contrast, neither an increase in blood pressure nor heart rate occurred in those patients' given fentanyl. It was concluded that nalbuphine 0.3 mg/kg was only partially effective in reducing the cardiovascular responses to laryngoscopy and intubation [24]. In the present study heart rate increased at laryngoscopy and intubation and at 1 min post intubation. Thereafter, the heart rate came to the baseline. There was a slight increase in heart rate in group N, but this increase was negligible as compared to saline group.

Chawada PM et al observed an increase in heart rate by 14.2% at laryngoscopy and intubation and at 1 min post intubation increase by 16.6%. The heart rate started decreasing 3 min post intubation and was almost equal to baseline at around 10 min post intubation. They concluded that nalbuphine 0.2 mg/kg prevented a marked rise in heart rate and mean arterial pressure associated with laryngoscopy and intubation[15]. Similar results were found in present study with respect to heart rate response to laryngoscopy and intubation. In their study, MAP had increased by 12.35% in control group and 4.39% in nalbuphine group. The increase in control group was higher compared to nalbuphine group at all times. In current study too increase in SBP was always higher in control group than nalbuphine group.

In the present study, none of the patients had significant adverse effects like arrhythmias, ECG changes, desaturation, bradycardia etc. The other side effects like nausea and vomiting were not noted. So, I.V. nalbuphine; 0.3 mg/kg and I.V. pentazocine; 0.5 mg/kg were devoid of any side effects which is comparable with the previous studies conducted by Sadafule NN et al[12] and Fating DR et al[14].

CONCLUSIONS

Thus, from the results of present study it is concluded that intravenous Nalbuphine in dose of 0.3 mg/kg, five minutes before induction of anaesthesia effectively attenuated cardiovascular response to laryngoscopy and endotracheal intubation as compared to pentazocine. So, nalbuphine is a better drug than pentazocine for attenuation of cardiovascular responses to laryngoscopy and intubation.

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