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A Comparative Study of Fentanyl And Nalbuphine on Hemodynamic Response to Laryngoscopy And Endotracheal Intubation In Patients Undergoing Surgery Under General Anaesthesia.

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Abstract
Background: *Hemodynamic responses associated with laryngoscopy and intubation can be deleterious in patients with underlying cardiovascular compromise. We compared the efficacy of drugs, namely, Nalbuphine and Fenatnyl in attenuating the reflex pressor response of the above mentioned manoeuvres.*
Materials and Methods*: Sixty patients in the age group of 18-60 years and belonging to ASA physical staus, either I or II, were randomized into two groups. Group F received fentanyl 1μg/kg and group N received nalbuphine 0.1mg/kg. Heart rate, blood pressure, oxygen saturation were recorded before administration of study drug, after administration of study drugs and then at 1, 3, 5 and 10 minutes of endotracheal intubation.*
Aims and Objectives
To study the effect of i.v fentanyl (1μg/kg) and i.v nalbuphine (0.1mg/kg) during laryngoscopy and intubation on
- *Heart rate*
- *Systolic blood pressure*
- *Diastolic blood pressure*
- *Mean arterial pressure*

Results: *Both the groups showed increased heart rates during intubation, but that was statistically insignificant (p >0.05). Fentanyl group demonstrated a 15.55% rise in heart rate at the time of intubation while nalbuphine group reported a 14.47% rise which is almost equal.*
Group N showed a significant rise in SBP and DBP during intubation compared to Group F. Maximum rise in SBP and DBP in Group N was 15.60% and 10.09% respectively, where as in Group F it was 6.12% and 7.06% respectively.
Conclusion: *To conclude, fentanyl appears to be better than nalbuphine when there is need to control haemodynamic response to laryngoscopy and intubation. It is concluded from our study that fentanyl appears to be better than nalbuphine when there is need to control hemodynamic responses to laryngoscopy and intubation.*
Keywords: *Fentanyl,Nalbuphine.*

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I. Introduction

Hemodynamic responses to laryngoscopy and endotracheal intubation are well documented. Mechanical stimulation of proprioceptors at the base of the tongue induces a reflex sympathetic response that manifests as tachycardia, hypertension and elevated plasma catecholamine levels.1 This pressor response, although, of no great consequence in normotensive subjects is potentially lethal in patients with underlying cardiovascular abnormalities. Left ventricular dysfunction, hypertensive crisis, pulmonary edema, cardiac dysrhythmias and myocardial ischaemia have been reported in susceptible population.2Although many agents like vasodilators, α agonists, opioids, calcium channel blockers and topical lidocaine have been frequently evaluated in attenuating the intubation associated hemodynamic responses, no ideal drug has yet been discovered.3,4,5 Respiratory depression, histamine release, neuroexcitatory and gastrointestinal disturbances further preclude the use of the aforementioned drugs.6,7Fentanyl, a rapidly acting, synthetic opioid with a high potency and short half-life has been reported to be effective in suppressing the hemodynamic perturbations associated with laryngoscopy and intubation.7 Nalbuphine is a semisynthetic opioid . It has agonist-antagonist action on μ, κ, δ receptors and has also been shown to be effective in blunting the pressor response.

	Group F	Group N	P-value
Age	48.60 ± 9.08	47.20 ± 8.22	0.554
Sex(M/F)	19/11	20/10	0.622
Weight	71.13 ± 10.56	67.50 ± 10.40	0.185

II. Aim & Objectives

The pressor response to laryngoscopy and intubation may be exaggerated and of serious consequence, especially in patients with hypertention and cardiovascular disease, so attenuation of this response is required. Hence aim of the study is to compare the degree of blunting of pressor response with i.v fentanyl (1 mcg/kg) and i/v nalbuphine (0.1 mg/kg) during laryngoscopy and endotracheal intubation under general anaesthesia.

III. Material & Methods

This was an observational study. After obtaining approval from the institutional ethics committee, 60 patients scheduled for surgery under general anesthesia were studied.
The patients were randomly divided into two groups-
Group F (n=30) : received inj. Fentanyl 1µg/kg (i.v)
Group N (n=30) : received inj. Nalbuphine 0.1mg/kg (i.v)
All patients were in the age group of 18-60 years , belonging to either sex and ASA physical status I or II.
Exclusion Criteria-

- Patient refusal
- Patients with ASA III or more.
- Mallampatti score III or more
- Those with significant respiratory, cardiovascular, renal, hepatic or endocrine disorders.
- Those with history of opioid addiction.
- Known allergy to study drugs.
- Morbidly obese (BMI >35)
- Intubation more than 1 attempt or prolonged laryngoscopy (>15sec).

A detailed pre anesthetic evaluation for each case was done. Routine and special investigations were ordered. All patients were kept nil orally for atleast 8- 10 hours prior to the surgery. Patients were given tab alprazolam 0.25 mg and tab pantoprazole 40 mg bed time, night before the surgery. Pre-operative vitals were recorded (Heart rate, Blood pressure, SPO2) . The study drugs Nalbuphine (0.1mg/kg) and Fentanyl (1µg/kg) , were administered in a double blind manner. After oxygenation, induction was done with iv propofol (2-2.5mg/kg) and iv rocuronium (0.6mg/kg). Laryngoscopy and intubation were performed after 5 minutes of administration of study drugs. Anaesthesia was maintained with O2:NO and isoflurane. Bolus doses of Rocuronium (0.1mg/kg) were used to maintain neuromuscular blockade.Heart rate, blood pressure (SBP, DBP, MAP) and SPO2 were monitored continuously and recorded before giving the study drug, after giving the study drug, at intubation, and then at 1, 3, 5 and 10 minutes post intubation.At the end of the surgery, anesthesia was reversed with inj. Neostigmine 0.05mg/kg and inj. Glycopyrrolate 0.01mg/kg i.v.Patients were observed intraoperatively as well as postoperatively for arrhythmias, bradycardia, respiratory depression, pruritis etc.

IV. Observation And Results

There was no statistical difference between the two groups with respect to age, weight, gender and ASA of the patients. Induction time (sec) was faster in Sevoflurane group (48.4±5.04) as compared to Propofol group (60.2±6.23) with a ($p<0.001$), which is highly significant. Also, the intraoperative haemodynamic parameters consisting of heart rate and blood pressure were comparable between the two groups with no statistically significant difference.

Table 1: Group comparison of age , sex and weight.
After laryngoscopy and intubation, both the groups showed elevations in HR. The greatest rise was 15.5% for group F and 14.4% for group N , both reported 1 minute post intubation.(Table 2) However, the changes in HR, at any time interval were not statistically significant ($p>0.05$).

Table 2: Group comparison of heart rate (beats/min)

Time interval	Mean ± Standard Deviation		Group F % change from baseline	Group N % change from baseline	p- value	Remarks
	Group F	Group N				
Base Line	81.47 ± 6.33	84.07 ± 6.77	-	-	0.130	NS
Induction	80.13 ± 6.64	83.17 ± 6.90	(-) 1.64	(-) 1.07	0.088	NS

1 min. after intubation	94.13 ± 8.84	96.23 ± 7.53	15.55	14.47	0.294	NS
3 min. after intubation	90.53 ± 7.49	92.83 ± 8.89	11.13	10.43	0.283	NS
5 min. after intubation	86.77 ± 7.97	89.80 ± 8.77	6.51	6.82	0.166	NS
10 min. after intubation	85.33 ± 7.37	84.37 ± 5.80	4.75	0.36	0.575	NS

NS: Non-significant
S: Significant

During induction, the heart rate in both the groups decreased from basal values of 81.47 to 80.13 bpm in fentanyl group, whereas in nalbuphine group, it decreased from 84.07 to 83.17 bpm. This decrease in mean heart rate in both the groups was statistically non-significant. Rise of mean heart rate at 1 min. after intubation was high in fentanyl group as compared to nalbuphine group. At 3min, 5min and 10min after intubation, there was fall of mean heart rate values in both the groups as compared to 1 min after intubation. In general, the highest change in heart rate from the baseline was recorded as 15.55 and 14.47 per cent at 1 min after intubation in fentanyl and nalbuphine group, respectively, however, in both groups there was no negative change i.e. decrease in heart rate from the base line except at induction. These values indicated better control of heart rate in both the groups.

Maximum rise in SBP was observed at 1 minute of intubation.(Table 3) For group N, it was 15.6%,while for group F it was 6. 12%. Percentage rise from the baseline values, at all times, post intubation was significantly high for the Nalbuphine group ($p < 0.05$).

Table 6: Group comparison of SpO2 (%)

Time interval	**Mean ± Standard Deviation**		**Group F**	**Group N**	**p- value**	**Remarks**
	Group F	**Group N**	**% change from baseline**	**% change from baseline**		
Base Line	99.70 ± 0.47	99.63 ± 0.61	-	-	0.638	NS
Induction	99.67 ± 0.48	99.60 ± 0.50	(-) 0.03	(-) 0.03	0.599	NS
1 min. after intubation	99.87 ± 0.35	99.77 ± 0.43	0.17	0.13	0.325	NS
3 min. after intubation	99.80 ± 0.41	99.73 ± 0.45	0.10	0.10	0.549	NS
5 min. after intubation	99.77 ± 0.43	99.73 ± 0.45	0.07	0.10	0.770	NS
10 min. after intubation	99.70 ± 0.47	99.67 ± 0.48	0.00	0.03	0.786	NS

NS: Non-significant
S: Significant

The data presented reveal that the two study groups were comparable and statistically non-significant. The mean SpO2 at the baseline were 99.70 and 99.63 % in fentanyl and nalbuphine group, respectively. During induction the mean SpO2 in both the groups was lower as compared to baseline and thereafter increased at all the time intervals after intubation except at 10 minutes after intubation in fentanyl group at which mean SpO2 returned to baseline. Percent change in mean SpO2 from baseline was recorded highest at 1 minute after intubation in both the groups and the change was high in fentanyl group at 1 and 3 minutes after intubation and in nalbuphine group at 5 and 10 minutes after intubation after which per cent change in mean SpO2 decreased and returned to baseline values in fentanyl group, whereas in nalbuphine group it was high as compared to baseline

Table 3: Group comparison of systolic blood pressure (mmHg)

Time interval	**Mean ± Standard Deviation**		**Group F**	**Group N**	**p- value**	**Remarks**
	Group F	**Group N**	**% change from baseline**	**% change from baseline**		
Base Line	118.77 ± 6.00	116.03 ± 7.71	-	-	0.131	NS
Induction	118.57 ± 7.88	115.17 ± 5.47	(-) 0.17	(-) 0.75	0.024	S
1 min. after intubation	126.03 ± 6.86	134.13 ± 8.72	6.12	15.60	0.000	S
3 min. after	124.73 ± 8.70	130.83 ± 4.86	5.02	12.75	0.000	S

intubation						
5 min. after intubation	119.83 ± 5.53	127.63 ± 5.69	0.90	10.00	0.000	S
10 min. after intubation	117.90 ± 4.92	126.30 ± 6.77	(-) 0.73	8.85	0.000	S

NS: Non-significant
S: Significant

Similarly , Nalbuphine group demonstrated persistently higher levels of DBP.(Table 4) Even At 10 minutes of intubation, group N continued to show a 5.07% rise of DBP, while a 0.42% fall was reported for the fentanyl group. This difference was statiscally significant ($p < 0.05$).

Table 4: Group comparison of diastolic blood pressure (mmHg)

Time interval	Mean ± Standard Deviation		Group F	Group N	p- value	Remarks
	Group F	Group N	% change from baseline	% change from baseline		
Base Line	80.23 ± 6.85	80.90 ± 6.83	-	-	0.665	NS
Induction	80.07 ± 7.70	80.77 ± 5.07	(-) 0.21	(-) 0.16	0.581	NS
1 min. after intubation	85.90 ± 9.96	89.07 ± 8.28	7.06	10.09	0.020	S
3 min. after intubation	83.13 ± 4.51	87.20 ± 7.99	3.61	7.79	0.002	S
5 min. after intubation	82.67 ± 6.48	85.63 ± 6.97	3.03	5.85	0.051	S
10 min. after intubation	79.90 ± 4.88	85.00 ± 5.48	(-) 0.42	5.07	0.000	S

NS: Non-significant S : Significant.

Also, mean MAP levels were significantly high in the nalbuphine group.(Table 5)

Table 5: Group comparison of mean arterial pressure (mmHg**)**

Time interval	Mean ± Standard Deviation		Group F	Group N	p-value	Remarks
	Group F	Group N	% change from baseline	% change from baseline		
Base Line	93.17 ± 3.04	91.33 ± 5.05	-	-	0.563	NS
Induction	92.93 ± 6.51	90.90 ± 5.76	(-) 0.25	(-) 0.36	0.429	NS
1 min. after intubation	99.23 ± 6.73	102.77 ± 7.89	6.51	12.43	0.000	S
3 min. after intubation	97.03 ± 5.53	100.37 ± 6.13	4.15	9.98	0.000	S
5 min. after intubation	95.03 ± 4.53	98.33 ± 3.54	2.00	7.60	0.000	S
10 min. after intubation	92.47 ± 3.59	97.43 ± 4.78	(-) 0.75	6.81	0.000	S

NS: Non-significant
S: Significant

The values of mean MAP at induction showed decrease in both the groups as compared to baseline and were statistically significant. At 1 minute after intubation, mean MAP was 99.23 and 102.77 mmHg as compared to 93.17 and 91.33 mmHg during baseline in fentanyl and nalbuphine group, respectively. At 3 and 5 minutes after intubation, there was increase in mean MAP in fentanyl group, however, at 10 minutes after intubation mean MAP was lower as compared to baseline in fentanyl group. Similarly, in nalbuphine group, mean MAP was higher at all the time intervals after intubation but at decreasing trend as compared to the baseline. Percent change in mean MAP in fentanyl group was recorded as 6.51, 4.15, 2.00 and -0.75 at 1, 3, 5 and 10 minutes after intubation, respectively. Similarly in nalbuphine group, per cent change in mean MAP was recorded as 12.43, 9.98, 7.60 and 6.81 at 1, 3, 5 and 10 minutes after intubation, respectively.

V. Discussion

Laryngoscopy and endotracheal intubation are mandatory for most patients undergoing surgery under general anaesthesia. They may be associated with transient but marked increase in blood pressure and heart rate, attributable to a reflex sympathoadrenal response.8 In the absence of any specific preventive measures, intubation associated elevations of heart rate could be as high as 20-45%. While a 36-45% rise in systolic blood pressure has been reported by many researchers.9,10

Vasodilators, alpha 2 agonists, calcium channel blockers have all provided means of attenuating the pressor response. These agents, however have limitations. Besides having no role in induction and maintenance of anesthesia, they can also lead to serious complications.11-17 Narcotics while maintaining the depth of anaesthesia, can attenuate the pressor response effectively. Fentanyl is readily available in our country and has a rapid onset and short duration of action. The onset of action of Nalbuphine is between 2-3minutes. It is cardio-stable and produces minimal side effects in the dose range of 0.2-0.4 mg/kg.Kay et al, found complete attenuation of pressor response with 5μg/kg fentanyl. However, such large doses were associated with muscular rigidity, bradycardia, nausea and vomiting.18 In the present study, optimal doses of the study drugs were selected based upon the assumption that nalbuphine is equipotent to morphine and fentanyl on a mg basis is 80 times more potent than morphine.19 Thus, doses of 1μg/kg fentanyl and 0.1mg/kg nalbuphine were considered appropriate.Ko et al, in their study, concluded that in order to effectively blunt the pressor response, fentanyl must be administered 5 minutes before tracheal intubation.20 In our study, both fentanyl and nalbuphine were given 5 minutes prior to intubation.In a study conducted by Khan and Hameedullah, HR decreased in the fentanyl group. While in the Nalbuphine group, it remained significantly high.19 In our case, a slight and insignificant fall in heart rate was observed at the time of induction for both the groups. Post-intubation , the levels rose . However the changes reported at all time intervals were insignificant ($p > 0.05$).

After administration of the study drugs, Nalbuphine group reported a fall in Systolic Blood Pressure. However, 1 minute post intubation a 15.6% increase from the baseline value was recorded for the same group. Fentanyl group, on the other hand, showed only a 6.12% increase. This difference was statiscally significant. More so, the levels of SBP for nalbuphine group were significantly high even 10 minutes post intubation. Similarly, levels of DBP remained significantly high in group N compared to group F. Khan et al, reported similar findings and suggested that nalbuphine provided lesser control of the pressor response.19 Percentages changes in mean MAP following intubation for the fentanyl group were +6.51, +4.15, + 2.00 and -0.75 at 1, 3, 5 and 10 minutes. Whereas, for the nalbuphine group, the changes were recorded as +12.43, +9.98, +7.60, +6.81 at similar intervals. On comparison, Group N demonstrated significantly higher mean MAP levels ($p<0.05$).

Weiss BM et al, compared fentanyl and nalbuphine in patients of coronary artery bypass surgery. It was found, that all patients given nalbuphine required nitroglycerine to control arterial blood pressure. At 2 minutes post intubation, plasma levels of epinephrine, norepinephrine, vasopressin and cortisol did not change in the fentanyl group while they increased in the nalbuphine group.21

In general, post intubation SBP, DBP and MAP were elevated in both the groups. however, significantly higher values were recorded for the nalbuphine group. These elevations persisted for 3-5 minutes after which the values started falling toward the baseline levels. Aftab et al, while comparing fentanyl/isoflurane and nalbuphine/isoflurane in patients undergoing coronary artery bypass , concluded that fentanyl provided better hemodynamic stability.22Kay et al, found significant elevations of HR & BP in the nalbuphine group and neither an increase in HR nor BP in the fentanyl group.18No patient from either group reported bradycardia, nausea, vomiting, respiratory depression, arrhythmia, pruritis etc

VI. Conclusion

Narcotics while maintaining the depth of anaesthesia, can attenuate the pressor response effectively. Fentanyl is readily available in our country and has a rapid onset and short duration of action. The onset of action of Nalbuphine is between 2-3minutes. It is cardio-stable and produces minimal side effects in the dose range of 0.2-0.4 mg/kg. In the present study, optimal doses of the study drugs were selected based upon the assumption that nalbuphine is equipotent to morphine and fentanyl on a mg basis is 80 times more potent than morphine.19 Thus, doses of 1μg/kg fentanyl and 0.1mg/kg nalbuphine were considered appropriate. We concluded from our study that fentanyl appears to be better than nalbuphine when there is need to control hemodynamic responses to laryngoscopy and intubation.

Conflicts of intrest:

There are no conflicts of interest.

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