



Original Research Article

Comparison of fentanyl, clonidine and nalbuphine for attenuation of pressor response during endotracheal intubation under general anaesthesia

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ABSTRACT

Background: Increased sympathoadrenal activity invariably occurs during endotracheal intubation. Various drugs have been used to obtund this pressor response. This study was done to find out most favourable drug among fentanyl, nalbuphine and clonidine for prevention of this pressor response.

Materials and Methods: This was a randomized, prospective study involving ninety patients of ASA grade 1, equally divided into three groups. Group F, C and N received fentanyl 2 mcg/kg, Clonidine 2 mcg/kg and nalbuphine 2mg/kg i.v respectively, 5 minutes prior to induction. Vitals parameters were noted at frequent intervals Chi square test and Anova test were used for statistical analysis. P value <0.05 was considered as statistically significant.

Results: Maximum increase in heart rate and blood pressure was seen at the time of intubation in F and N groups, whereas decrease in these parameters occurred with clonidine, difference was found to be statistically significant. Haemodynamic stability was seen in F and N group after 5 minutes of intubation. Clonidine showed maximum decrease in heart rate and systolic as well as diastolic blood pressure at all time intervals from intubation as compared to other two groups.

Conclusion: In this study it was found that Clonidine produced an earlier and more stable haemodynamics as compared to Fentanyl and Nalbuphine, and it can be concluded that Clonidine given intravenously in doses of 2 mcg/kg 5 minutes prior to intubation is superior to Fentanyl and Nalbuphine in preventing haemodynamic changes at the time of laryngoscopy and intubation.

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1. Introduction

Laryngoscopy and endotracheal intubation are associated with stressful stimuli that provoke tachycardia, hypertension, arrhythmias due to increased sympathoadrenal activity¹ which may be detrimental in patients with cardiovascular disease, congestive heart failure (CHF), geriatric population and cerebral haemorrhage.

To blunt this pressor response various drug regimens have been tried including opioids, barbiturates, benzodiazapines, beta blockers, calcium channel blockers, vasodilators but each drug has its own shortcoming^{2–7}

Clonidine an alpha 2 adrenergic agonist causes an increase in cardiac baroreceptor reflex sensitivity and also decreases the sympathetic nervous system outflow from CNS to peripheral tissues and has been used for attenuation of pressor response.^{8,9}

Fentanyl, a synthetic narcotic analgesic, has rapid onset and short duration of action which is a routinely used for intravenous analgesia. It has proved to be very effective to control short term hemodynamic change.¹⁰ Nalbuphine an agonist antagonist opioid which acts on mu, kappa and delta receptors is used to blunt hemodynamic response to laryngoscopy and orotracheal intubation due to its properties of providing cardiovascular stability, longer analgesia and no respiratory depression.^{11–13} These drugs

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have been studied and compared individually and amongst each other but have never been studied together in similar set of patients. The purpose of this study was to compare Fentanyl, Nalbuphine and Clonidine for attenuation of pressor response due to laryngoscopy and intubation.

2. Materials and Methods

A prospective study was done involving 90 adult patients of age group 18-50 years, ASA grade 1 and 2, Mallampati grade 1 and 2 who were posted for surgery under general anaesthesia. Research proposal was submitted to and approved by ethical committee. A thorough pre-anaesthetic evaluation was done, after written informed consent. Pregnant patients, patients having history of cardiovascular, renal or hepatic disease; allergy to opioids and in whom difficult intubation was anticipated, were excluded from the study.

Patients were randomly distributed into 3 groups (30 each) by computerized random allocation. Study drugs were given 5 minutes prior to laryngoscopy, Fentanyl 2.0 mcg/kg (Group F), Clonidine 2.0 mcg/kg (Group C), Nalbuphine 0.2 mg/kg (Group N). All standard ASA monitors were attached and continuously monitored. Intravenous Inj. midazolam 2mg and Inj. glycopyrrolate in dose of 0.02mg/kg was given as premedicants. After preoxygenation with 100% oxygen, induction was done with Inj. Propofol (2mg/kg). Inj. Vecuronium 0.1 mg/kg i.v was used to facilitate intubation. oxygen and nitrous oxide in ratio of 40:60, isoflurane (0.5-1.5%) and intermittent Vecuronium was used for maintainance of anaesthesia. For first 10 minutes post intubation no other drug or surgical stimulus was given to the patients. In patients where laryngoscopy time was more than 30 seconds or in whom a second attempt was required were excluded.

Heart rate, systolic blood pressure and diastolic blood pressure were noted at the time intervals starting with baseline parameters (BL), during intubation (Ti) and then at one minute (T1), three minutes (T3), five minutes (T5) and ten minutes (T10) after intubation. After recording the parameters at the above mentioned intervals, surgery was started. Sample size of 30 in each group was calculated on basis of pilot study. Data was analysed using SPSS v21. Categorical data was represented as frequencies & percentages. Continuous data was represented as mean & standard deviation. Chi square test was used as test of significance for categorical data. Anova test was used as test of significance for comparison of means between three groups. P value <0.05 was considered as statistically significant. Line diagrams were drawn to represent the trend over a period of time.

3. Results

There was no statistical difference among the three groups with respect to the demographic variables (age, weight and gender) of patients. (Table 1)

During intubation(Ti) maximum change in heart rate was seen in group F (Fentanyl group, % change from baseline +17.44%) whereas group C (Clonidine group) showed decrease in heart rate (- 4.2%) while group N (Nalbuphine) group had an increase of 14.8%. This difference was statistically significant between the three groups. At 1 minute (T1) and 3 minutes (T3) after intubation there was increase in HR in group F (+15.9 and +6.4) and group N (+13.4% and +5.7%), with more increase in group F, whereas in group C there was decrease in HR (-5.2% and -8.2%). There was statistical difference between F and C, C and N while there was no statistical difference between F and N. At 5 minutes after intubation (T5) there was decrease in HR in all the groups with maximum decrease in group C (-8.5%). This was statistically significant difference among the groups. At 10 min after intubation (T10) there was decrease in HR in all the groups with more decrease in groups C and N while it was less in group F (-5.3%). This was statistically non significant among the groups. (Tables 2 and 3)

At Ti maximum increase in SBP was in group F (+10.4%) while in group C there was decrease in SBP (-4.3%). This was statistically significant between F and C, C and N but not between F and N. At T1 and T3 maximum increase in SBP was in group F while there was decrease in SBP in group C. This was statistically significant among F and C, C and N but not between F and N. At T5 there was increase in SBP in groups F and N with more increase in group F while there was marked decrease in group C (-18.7%). The changes were statistically significant among all the groups. At T10 there was decrease in SBP in all the groups with more decrease in group C. This was also statistically significant among all the groups. (Tables 4 and 5)

At Ti there was increase in DBP in F and C groups with maximum increase in group F. (12,3%). There was slight decrease in group C. This was statistically significant between F and N, C and N but not between F and C. At T1 and T3 there was increase in DBP in group F and N with more increase in group F while there was decrease in group C. This was statistically significant among group F and C, C and N but not between F and N (at T1) while at T3 this was statistically significant among all the groups. At T 5 there was increase in DBP in group F & N while decrease in group C. This was statistically significant among all the groups. At T10 there was decrease in DBP in all the three groups. Maximum decrease was seen in group C (-15.3%) This was statistically significant between group F & C and F & N while not significant between C & N. (Tables 6 and 7)

Table 1: Demographic data

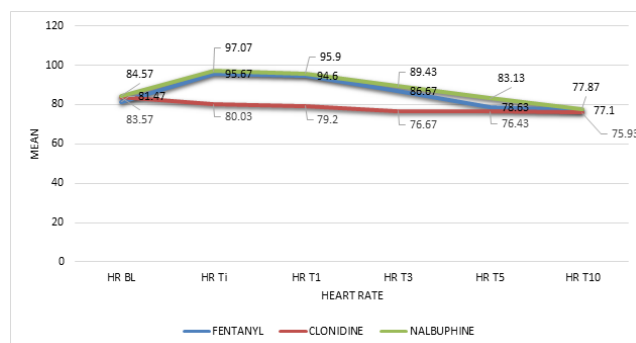
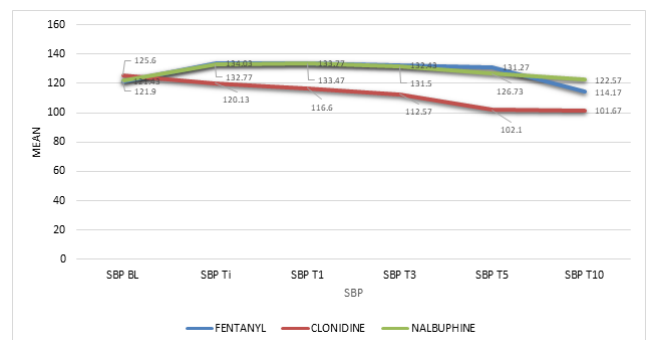
	Group F (n=30)	Group C (n=30)	Group N (n=30)	P value
Age, years (Mean \pm SD)	46.667 \pm 5.46	46.60 \pm 4.47	46.533 \pm 5.12	0.995 (NS)
Weight, kgs (Mean \pm SD)	57.667 \pm 6.22	57.667 \pm 6.22	57.667 \pm 6.22	1.000 (NS)
Female/Male (n)	21/9	19/11	16/14	0.407 (NS)

Table 2: Heart Rate (HR) at different time intervals

Time	Group	n	Mean	SD	P value	Post HOC tests P value
BL	Fentanyl	30	81.467	10.1463	0.360	F&C = 0.342
	Clonidine	30	83.567	6.3717		F&N = 0.162
	Nalbuphine	30	84.567	8.6091		C&N = 0.650
Ti	Fentanyl	30	95.667	10.3854	0.001	F&C = 0.001
	Clonidine	30	80.033	6.3869		F&N = 0.002
	Nalbuphine	30	97.067	9.3379		C&N = 0.001
T1	Fentanyl	30	94.666	8.8565	0.001	F&C = 0.001
	Clonidine	30	79.200	6.5517		F&N = 0.549
	Nalbuphine	30	95.900	11.0514		C&N = 0.001
T3	Fentanyl	30	86.667	8.8759	0.001	F&C = 0.001
	Clonidine	30	76.667	7.1647		F&N = 0.200
	Nalbuphine	30	89.433	8.7402		C&N = 0.001
T5	Fentanyl	30	78.633	7.7035	0.001	F&C = 0.001
	Clonidine	30	76.433	6.2790		F&N = 0.017
	Nalbuphine	30	83.133	7.4080		C&N = 0.001
T10	Fentanyl	30	77.100	10.2800	0.862	F&C = 0.608
	Clonidine	30	75.933	7.2347		F&N = 0.918
	Nalbuphine	30	77.867	8.5167		C&N = 0.681

Table 3: Percentage change from baseline in HR at different time intervals

Time	Group F	% change	Group C	% change	Group N	% C hange	P value
Baseline	81.46		83.56		84.56		0.360
Ti	95.66	+17.44	80.03	-4.2	97.06	+14.8	0.001
T1	94.66	+15.9	79.20	-5.2	95.90	+13.4	0.001
T3	86.66	+6.4	76.66	-8.2	89.43	+5.7	0.001
T5	78.63	-3.5	76.43	-8.5	83.13	-1.7	0.001
T10	77.10	-5.3	75.93	-9.1	77.86	-7.9	0.862

**Fig. 1:** Trend of heart rate with different drugs during study period**Fig. 2:** Trend of systolic blood pressure with different drugs during study period

4. Discussion

Most of the patients undergoing surgery under general anaesthesia require endotracheal intubation. Laryngoscopy

Table 4: Systolic Blood Pressure (SBP) at different time intervals

Time	Groups	n	Mean	SD	P value	Post HOC tests P value
BL	Fentanyl	30	121.433	12.0650	0.145	F&C = 0.073
	Clonidine	30	125.600	5.9283		F&N = 0.839
	Nalbuphine	30	121.900	7.5171		C&N = 0.111
Ti	Fentanyl	30	134.033	11.8307	0.001	F&C = 0.001
	Clonidine	30	120.133	9.2726		F&N = 0.621
	Nalbuphine	30	133.467	8.2323		C&N = 0.001
T1	Fentanyl	30	133.767	8.7914	0.001	F&C = 0.001
	Clonidine	30	116.600	10.7530		F&N = 0.898
	Nalbuphine	30	132.767	7.3284		C&N = 0.001
T3	Fentanyl	30	132.433	7.2952	0.001	F&C = 0.001
	Clonidine	30	112.567	10.4640		F&N = 0.659
	Nalbuphine	30	131.500	6.1012		C&N = 0.001
T5	Fentanyl	30	131.933	5.5518	0.001	F&C = 0.001
	Clonidine	30	102.100	14.7235		F&N = 0.038
	Nalbuphine	30	126.733	5.0236		C&N = 0.001
T10	Fentanyl	30	114.167	12.3291	0.001	F&C = 0.001
	Clonidine	30	101.667	6.4560		F&N = 0.001
	Nalbuphine	30	121.567	6.5162		C&N = 0.001

Table 5: Percentage change from baseline in (SBP) at different time intervals

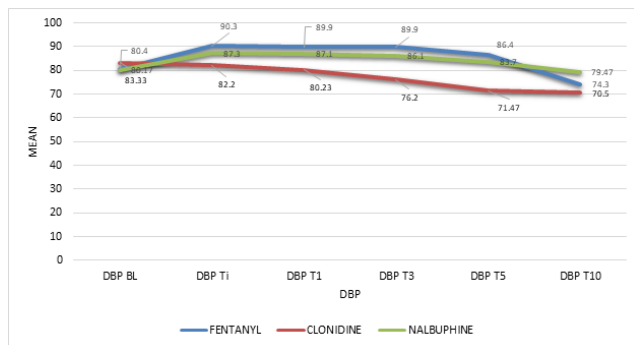
Time	Group F	% change from basal value	Group C	% change from basal value	Group N	% change	P value
Baseline	121.43		125.60		121.90		0.145
Ti	134.03	+10.4	120.13	-4.3	133.46	+9.5	0.001
T1	133.76	+10.1	116.60	-7.1	132.76	+8.9	0.001
T3	132.43	+9.1	112.56	-10.4	131.50	+7.9	0.001
T5	131.93	+8.6	102.10	-18.7	126.73	+3.9	0.001
T10	114.16	-5.9	101.66	-19.1	121.56	-0.3	0.001

Table 6: Diastolic Blood Pressure (DBP) at different time intervals

Time	Groups	n	Mean	SD	P value	Post HOC tests P value
BL	Fentanyl	30	80.400	6.2511	0.087	F&C = 0.066
	Clonidine	30	83.333	5.9616		F&N = 0.883
	Nalbuphine	30	80.167	6.1030		C&N = 0.048
Ti	Fentanyl	30	90.33	7.6546	0.001	F&C = 0.272
	Clonidine	30	82.20	4.7590		F&N = 0.001
	Nalbuphine	30	87.30	6.1552		C&N = 0.003
T1	Fentanyl	30	89.90	7.0255	0.001	F&C = 0.001
	Clonidine	30	80.23	5.8054		F&N = 0.419
	Nalbuphine	30	87.10	5.1404		C&N = 0.001
T3	Fentanyl	30	88.56	6.7126	0.001	F&C = 0.001
	Clonidine	30	76.20	5.2021		F&N = 0.001
	Nalbuphine	30	86.10	4.6989		C&N = 0.001
T5	Fentanyl	30	86.40	6.7688	0.001	F&C = 0.001
	Clonidine	30	71.48	5.2898		F&N = 0.001
	Nalbuphine	30	83.70	6.0841		C&N = 0.001
T10	Fentanyl	30	74.300	6.2596	0.001	F&C = 0.001
	Clonidine	30	70.53	5.4233		F&N = 0.001
	Nalbuphine	30	79.46	6.5777		C&N = 0.154

Table 7: Percentage change from baseline in DBP at different time intervals

Time	Group F	% change	Group C	% change	Group N	% change	P value
Baseline	80.40		83.33		80.16		0.087
Ti	90.33	+12.3	82.20	-1.3	87.30	+8.9	0.001
T1	89.90	+11.8	80.23	-3.7	87.10	+8.6	0.001
T3	88.56	+10.1	76.20	-9.8	86.10	+7.4	0.001
T5	86.40	+7.4	71.48	-14.2	83.70	+4.4	0.001
T10	74.30	-7.6	70.53	-15.3	79.46	-0.8	0.001

**Fig. 3:** Trend of systolic blood pressure with different drugs during study period

performed for intubation causes sympathetic stimulation which causes increase in blood pressure as well as heart rate.¹ Upto 36 to 45% increase in systolic blood pressure and 20 to 45% increase in heart rate of baseline value may occur, if no specific preventive measures are undertaken.^{14,15} Some patients may even develop arrhythmias. Various agents like calcium channel blockers, vasodilators, alpha 2 agonists, narcotics have been used to attenuate the pressor response to laryngoscopy and intubation.²⁻⁷ Narcotics like fentanyl and nalbuphine, besides obtunding the haemodynamic response to intubation, also have advantage of maintaining depth of anaesthesia. Fentanyl, a pure agonist, acts on mu receptors.¹⁶ It's onset of action is rapid and duration of action is short. It causes increase in parasympathetic tone while decreasing sympathetic tone.

Clonidine is an alpha 2 receptor agonist which has been used previously as an anti hypertensive agent and also used as an agent to blunt pressor response due to laryngoscopy and intubation. As shown by Zalundro et al. intravenous clonidine was better than oral clonidine in attenuating the pressor response.¹⁷ Bhalereo et al found that Clonidine given i.v as premedicant was effective in preventing stress induced haemodynamic response.¹⁸ Chawda, Pareek and Mehta found that 0.2mg/kg of nalbuphine given 3-5 minutes before intubation is effective in preventing the pressor response.¹⁹ Effectivity of Nalbuphine in dose of 0.2 mg/kg in achieving acceptably stable vital parameters and good anesthetic effect were proved by study of Nath R et al.²⁰ These drugs have been studied and compared individually

and amongst each other but have never been studied together in similar set of patients.

Study by Ko et al.²¹ concluded that optimal time to give Fentanyl so as to prevent pressor response to intubation was 5 minutes before intubation. In our study also, drugs were given 5 minutes prior to intubation. 5 microgram per kilogram (mcg/kg) body weight of Fentanyl can effectively obtund the haemodynamic response to laryngoscopy as found by Kay et al.²² but at the expense of side effects like nausea vomiting, muscular rigidity and bradycardia. Apnoeic episodes were seen by McClain in 4 patients with doses of 3.2 to 6.5 micro/kg of Fentanyl.²³ We decided to use a dose of 2.0 mcg/kg of Fentanyl to prevent pressor response. Study by Yushi et al. found that Fentanyl in a dose of 2microgram/kg is effective in suppressing pressor response to endotracheal intubation.²⁴ Post operative respiratory depression may occur in surgeries lasting less than one hour with high doses of Fentanyl.^{25,26}

Gupta and Tank also found that Fentanyl given in dose of 2 mcg/kg before induction was effective in obtunding pressor response to endotracheal intubation and laryngoscopy.²⁷ However, they did not comment upon the optimum time for intubation after administration of the drug.

In our study, at the time of intubation, significant increase in heart rate was seen in F and N group whereas C group did not show any increase in heart rate (statistically significant) signifying that Clonidine was better in maintaining heart rate at the time of intubation.

Increase in heart rate in both groups (F,N) persisted at 3 minutes and gradually settled after 5 minutes. There was no significant variation in heart rate in group C throughout the observation period. Our findings of change in heart rate in F and N group are similar to those by Rawal and Wennhager.²⁸ Study by Ahsan et al on Nalbuphine also found gradual settlement of heart rate after intubation.¹⁵

Group C showed best control of HR as compared to Group F and Group N which is due to reduction in sympathetic outflow and increase in parasympathetic tone of central origin. The trend can be appreciated from Figure 1.²⁹ Our findings are supported by study by Dipak and Malini who found Clonidine was effective in attenuating pressor response to intubation.³⁰

There was increase in blood pressure in both F and N groups at the time of intubation, which persisted even after

3 and 5 minutes after intubation, while a slight decrease in blood pressure was observed in group C. Systolic blood pressure and diastolic blood pressure settled down to pre intubation levels after 10 minutes in group F and N where as maximum decrement was seen in group C (Figures 2 and 3). Our findings are in concordance with studies by Kalra NK et al.⁹ who found intravenous Clonidine was better in comparison to Magnesium sulphate in controlling blood pressure during laproscopic cholecystectomy. Study by Chaudhari M et al also found stastically significant increase in blood pressure and heart rate just after intubation in Nalbuphine group as compared to Clonidine group, corroborating our study findings.³¹ Our findings are also in concordance with Bhalereo et al. who found that Clonidine given i.v as premedicant was effective in preventing stress induced haemodynamic response.¹⁸

5. Conclusion

Obtundation of pressor response during laryngoscopy is important to reduce the morbidity associated with increased sympathoadrenal drive. In this study we found that all three agents, Fentanyl, Nalbuphine and Clonidine were effective in achieving the objective of controlling the haemodynamic response to stress of endotracheal intubation. However, Clonidine proved to be superior compared to the other two as, the latter took 5-10 minutes to reach stable haemodynamic parameters while, Clonidine produced more stable haemodynamics in lesser time when given in dose of 2.0 microgram per kilogram 5 minutes prior to intubation.

6. Limitation

Limitation of our study is that in post-operative period patients could have been assessed for sedation and analgesia in all the three groups.

7. Source of Funding

None.

8. Conflict of Interest

None.

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