

Original research article

## A Comparative Study of Oral Clonidine and Intravenous Fentanyl in Attenuation of The Hemodynamic Responses to Laryngoscopy and Endotracheal Intubation in a Tertiary Care Hospital

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### Abstract

**Introduction:** In anaesthesia, circulatory stimulation during tracheal intubation are caused by the stimulation of laryngeal and tracheal tissues from both direct laryngoscopy and placement of the ET tube in the trachea. These stimuli often evoke sympathoadrenal responses characterized by changes in Blood pressure, Heart rate, Cardiac rhythm, ST segment changes, and may lead to pulmonary oedema and rupture of cerebral aneurysm. In the present study that was carried out in the Institute, we compared the efficacy of Oral Clonidine versus Intravenous Fentanyl in attenuating the cardiovascular stress response to laryngoscopy and tracheal intubation.

**Material and Methods:** The present Prospective and Comparative study was carried out at a Tertiary Care Hospital amongst 100 patients those who were randomly allocated to two groups, Group C: Patients in this group received- 5 microgram/kg of Oral Clonidine with 2 sips of water 90 minutes prior to surgery. Group F: Patients in this group received 100ml of normal saline over 10 minutes and 2 microgram /kg of fentanyl in 5ml of normal saline, 5 minutes prior to laryngoscopy and intubation.

**Results:** Out of 100 subjects, 32% subjects were in the age group 21 to 30 years and 22% in 41 to 50 years. The mean heart rate during Laryngoscopy in the groups Fentanyl and Clonidine were 108.58 and 91.56 respectively. The mean SBP during Laryngoscopy in the groups Fentanyl and Clonidine was 139.84 and 124.78 respectively and the mean SBP at 1 minute after intubation was 137.14 and 121.94 respectively. The mean DBP during laryngoscopy in the groups Fentanyl and Clonidine were 91.18 and 82.68. and at 1 minute after intubation, it was 88.36 and 78.52 respectively. The mean MAP at 1 minute after intubation in the groups Fentanyl and Clonidine were 101.54 and 92.98 respectively

**Conclusion:** Oral Clonidine 5 µg/kg proved to keep the hemodynamics in stable manner during laryngoscopy and endotracheal intubation and up to 30 mins post-intubation. Fentanyl in the dosage of 2 µg /kg given 5 minutes before laryngoscopy and intubation attenuated the hemodynamic changes, but was not equally effective in reducing the increase in heart rate and blood pressure.

**Keywords:** Clonidine, laryngoscopy, Fentanyl, endotracheal intubation, pressor response

## Introduction

Endotracheal intubation to secure the airway is the most essential element of modern-day general anaesthesia practice. The benefits of doing so has been highlighted, clarified and praised over these years. But endotracheal intubation is not entirely harmless and we come across many numbers of complications associated with it ranging from relatively minor to the seriously grave and potentially life-threatening ones which would occur in susceptible patients.

Though, these complications could be traced down to any of the many procedures that are part and parcel of the sequence of induction of anaesthesia and intubation. Laryngoscopy and Endotracheal Intubation still remain the most powerful noxious stimuli which require a deeper level of anaesthesia than that is needed for surgical incision[1].

In anaesthesia, circulatory stimulation during tracheal intubation are caused by the stimulation of laryngeal and tracheal tissues from both Direct laryngoscopy and placement of the ET tube in the trachea. These stimuli often evoke sympathoadrenal responses characterized by changes in Blood pressure, Heart rate, Cardiac rhythm, ST segment changes, and may lead to pulmonary oedema and rupture of cerebral aneurysm.[2]

In anaesthetized humans, the usual circulatory responses to laryngeal and tracheal stimulation are tachycardia and hypertension. The response peaks at about 1 to 2 minutes and return to baseline within 5 to 10 minutes.[3] When planning the anaesthetic induction, these effects must be blunted to whatever degree is possible, especially, if the patient is in a high-risk population like patients with Uncontrolled hypertension, Coronary artery disease, Asthma, Elevated intracranial pressure, Cerebral aneurysm etc.[1]

Different techniques have been used to attenuate this hemodynamic response to laryngoscopy and intubation.

These include: -

- Topical anaesthesia of the oropharynx, [4]
- Intravenous lignocaine [4]
- Intravenous fentanyl [5][6] (Donal E. Martin (1982) proved the efficacy of a low dose fentanyl in blunting the pressor response to endotracheal intubation), [7]
- Alfentanil, [6]
- Sodium nitroprusside, [8]
- Beta-adrenergic blocking drugs, [9][10]
- Alpha-2-adrenergic agonists [11] (Ghignone et al (1987) observed that **Clonidine** 5 mcg/ kg was effective in blunting the reflex tachycardia associated with laryngoscopy and intubation than lidocaine –fentanyl pre-treatment, [12]
- Alpha and beta-blockers,
- Calcium channel blockers

Pharmacological modification has been considered as one of the most common ways to attenuate pressor response. Prof. Ward and king (1960) in their study documented myocardial ischemic changes due to reflex sympathoadrenal response with a mean increase in systemic pressure of about +40 mm of Hg even in normotensives following laryngoscopy and endotracheal intubation.

Prys-Roberts et al (1971) [2] showed that this response is even more exaggerated in hypertensive individuals. Considering all these factors, attenuation of hemodynamic response to laryngoscopy and endotracheal intubation will be a laudable objective and is definitely indicated.

In our study that was carried out in the Institute, we compared the efficacy of Oral Clonidine versus Intravenous Fentanyl in attenuating the cardiovascular stress response to laryngoscopy and tracheal intubation.

**Material and Methods:**

The present Prospective and Comparative study was carried out at a Tertiary Care Hospital after the approval from Ethics Committee of the Institution amongst 100 patients of the age group 18-60 of ASA I or II posted for elective surgery under General anaesthesia.

**Sample Size estimation:**

With  $\alpha$  of 0.05,  $\beta$  of 0.20 (power of 80%), using reference value of  $69.71 \pm 12.44$  (n= 35) of Heart Rate 2 minutes after Intubation in Oral Clonidine group cases as compared to  $76.86 \pm 12.76$  (n= 35) for among Intravenous Fentanyl group cases using below mentioned formula, the sample size calculated was 47.996 per group. However, since resources like patients, investigative tools, time for research exist in sufficient quantity, a minimum of 50 cases for each group was to be enrolled for the present study.

Where, Z Value form standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

$\alpha$ : The probability of type I error (significance level) is the probability of rejecting the true null

hypothesis. (0.05)

$\beta$ : The probability of type II error (1 – power of the test) is the probability of failing to reject the false null hypothesis. (0.20) (Z $\beta$ =0.84 for 95% CI)

$\mu_2 - \mu_1$ : The value of allowable difference is the true mean difference between the test drugs.

**Selection criteria:****Inclusion criteria:**

Patients belonging to American society of Anaesthesiologists Grade I and II, willing to participate, age between 18 and 60 years, patients with Modified Mallampatti scores I & II, planned for Elective Surgery under General anaesthesia.

**Exclusion criteria:**

following patients with American society of Anaesthesiologists Grade III and IV patients, age < 18 years and > 60 years, Patient Refusal, Emergency Surgeries, Patients with Modified Mallampatti scores III & IV and/or Patients with predicted difficult airway, Allergy to either Clonidine or Fentanyl, Patients on medications which alter Heart rate, Pulse rate, Blood pressure and drugs which have interactions with Clonidine and Fentanyl e.g. Beta Blockers, Diuretics, Ace inhibitors, Patients with co- existing cardiovascular, respiratory, hepato-renal and metabolic disorders

**Assessment:**

All patients were assessed by detailed history and physical examination supported by laboratory investigations, chest X-ray, electrocardiogram. A preoperative visit was made to allay the anxiety and to develop a good rapport.

**Randomization:**

The patients were randomly allocated to two groups of 50 each with the help of a computer-generated table of random numbers to receive following drugs:

Group C: Patients in this group received- 5 microgram/kg of Oral Clonidine with 2 sips of water 90 minutes prior to surgery.

Group F: Patients in this group received 100ml of normal saline over 10 minutes and 2 microgram /kg of fentanyl in 5ml of normal saline, 5 minutes prior to laryngoscopy and intubation.

All patients were advised to be nil orally after 10pm on the preoperative day.

On the day of surgery patients in Group (C) were given Tab. Clonidine 5 µg/kg with in the morning 90 minutes before the scheduled time of surgery.

On arrival in the operating room an 18-gauge intravenous cannula was placed and crystalloid was started. Patients were monitored with a non-invasive monitor throughout the study period. Monitored parameters include Heart rate, Blood pressure (Systolic, Diastolic and Mean arterial pressure), Oxygen saturation and Electrocardiogram.

All the patients were then pre-medicated with Inj. Glycopyrrolate 0.2mg iv dose and Inj. Midazolam 1mg iv dose prior to induction and after a stabilization period of 3 minutes a baseline heart rate, blood pressure (systolic, diastolic and mean arterial pressure) were recorded. These values were noted down as Pre-induction values (PI) or the Baseline values.

Group F patients were then given inj. Fentanyl 2mcg/kg 5 minutes prior to intubation.

All the patients were preoxygenated with 100% oxygen for 3 minutes. Patients were induced with Inj. Thiopentone sodium 5 mg/kg intravenously followed by Inj. Succinylcholine 1.5mg/kg body weight. A digital stopwatch was used to time the events.

Then just after induction the Heart rate, Blood pressure (Systolic, Diastolic and Mean arterial pressure) were recorded. These values were noted down as Post-induction values (PoI). Heart rate and Blood pressure (Systolic, Diastolic and Mean arterial pressure) were recorded during Laryngoscopy and Endotracheal Intubation (DL). All patients were intubated with appropriate size cuffed, portex endotracheal tube. And thereafter the Heart rate and Blood pressure (Systolic, Diastolic and Mean arterial pressure) were recorded at one, three, five, ten, twenty- and thirty-minutes post intubation (I-1, I-3, I-5, I-10, I20, I-30 respectively). Anaesthesia was maintained with nitrous oxide, oxygen and 0.2 - 0.5% of Isoflurane and the patient ventilated using intermittent positive pressure ventilation. Muscle relaxation was maintained with intravenous Vecuronium bromide 0.08 mg/ kg.

No surgical stimulation was allowed for five minutes after intubation. Intraoperatively, the hemodynamic parameters (Heart rate, Blood Pressure), Oxygen Saturation were continuously monitored at regular intervals.

Patients were also observed for side effects like hypotension, bradycardia, hypertension, tachycardia and arrhythmias intra-operatively. After completion of surgery, neuromuscular blockade was reversed with Inj. Neostigmine 0.04 mg/kg and Inj. Glycopyrrolate 0.008 mg/kg intravenously. Patients were extubated after thorough suctioning and shifted to postoperative ward.

Patients were followed up postoperatively at hourly intervals till 9 hours after administration of clonidine, keeping in mind the elimination half time of clonidine. Any untoward effects were observed for and noted.

The results obtained in the study were presented in tabulated manner. Results were systematically analysed by 't'-test to find out the significance between the groups and in the groups at different periods of study from the pre-induction (PI) basal value. A p- value of less than 0.05 was considered as statistically significant.

**RESULTS:**

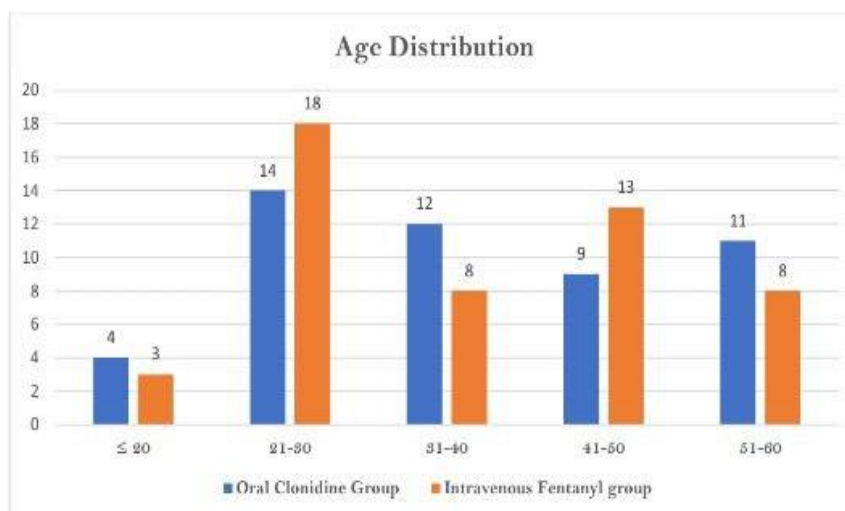
In our study that was carried out in the Institute, we compared the efficacy of Oral Clonidine versus Intravenous Fentanyl in attenuating the cardiovascular stress response to laryngoscopy and tracheal intubation.

**Table no.1: Distribution of patients according to their age.**

Age Group (years)	Intravenous Fentanyl Group n=50		Oral Clonidine Group n=50		Total %
	No.	%	No.	%	
≤ 20	3	6	4	8	7%
21 – 30	18	36	14	28	32%
31 – 40	8	16	12	24	20%
41 – 50	13	26	9	18	22%
51 – 60	8	16	11	22	19%
Total	50	100	50	100	100%

**p value = 0.619 (No significant difference)**

Out of 100 subjects, 7% were in the age less than 20 years, 32% subjects were in the age group 21 to 30 years, 20% were in the age group 31 to 40 years and 22% were with the age group 41 to 50 years, 19% were in the age group 51 to 60 years. Thus, there is no significant difference between the 2 groups as their **p=0.619** (p value of significance being < 0.05).

**Chart 1: Bar Chart showing age distribution in the study group.****Table no.2: Comparison of Mean Heart Rate (per min.) in two groups.**

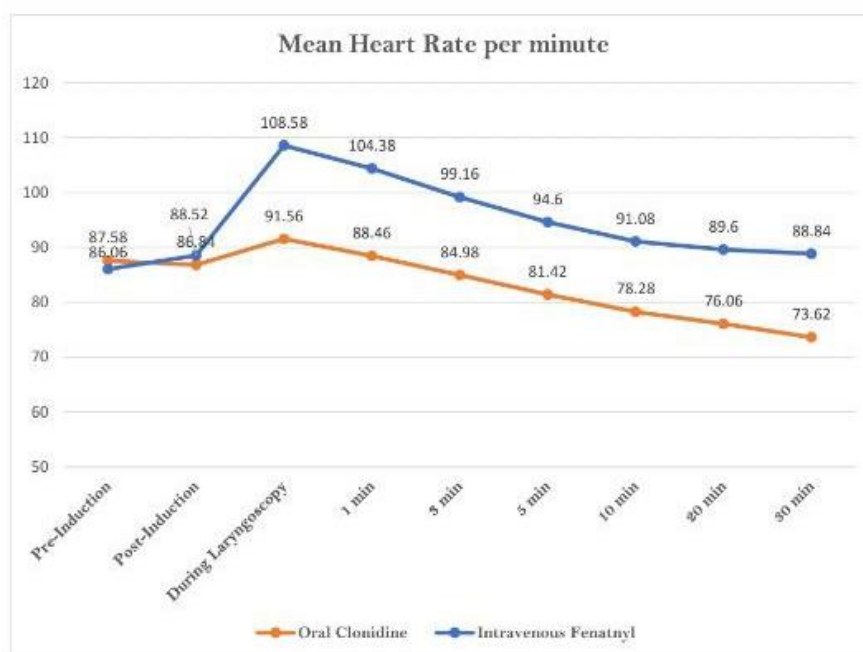
Time (Min.)	Intravenous Fentanyl Group n=50		Oral Clonidine Group n=50		P Value	Summary
	Mean	SD	Mean	SD		
Pre-Induction / Baseline	89.06	±12.22	87.58	±11.95	0.531	N.S
Post Induction / Pre- Laryngoscopy	88.52	±12.27	86.84	±11.82	0.488	N.S
During Laryngoscopy	108.58	±10.16	91.56	±11.07	0.001	Significant

1 min	104.38	±12.96	88.46	±10.13	0.001	Significant
3 min	99.16	±12.30	84.98	±9.25	0.001	Significant
5 min	94.60	±12.42	81.42	±8.59	0.001	Significant
10 min	91.08	±11.80	78.28	±8.04	0.001	Significant
20 min	89.60	±10.68	76.06	±7.61	0.001	Significant
30 min	88.84	±10.24	73.62	±7.65	0.001	Significant

\*N.S – Not Significant

The mean values of Baseline Heart rate in the groups Fentanyl and Clonidine were 86.06 and 87.58 respectively.

The mean Heart rate Post-induction/Pre-laryngoscopy in the groups Fentanyl and Clonidine were 88.52 and 86.84 respectively and p value 0.488 is statistically non-significant. The mean Heart rate during Laryngoscopy in the groups Fentanyl and Clonidine were 108.58 and 91.56 respectively and p value 0.001 is statistically significant. The mean Heart rate at 1 minute after intubation in the groups Fentanyl and Clonidine were 104.38 and 88.46 respectively and p value 0.001 is statistically significant. The mean Heart rate at 30 minutes after intubation in the groups Fentanyl and Clonidine were 88.84 and 73.62 respectively and p value 0.001 is statistically significant



**Chart 2: Trend chart showing Mean Heart Rate (per minute) at various intervals in both the groups**

**Table no.3: Comparison of Mean Systolic Blood Pressure (mmHg) in two groups.**

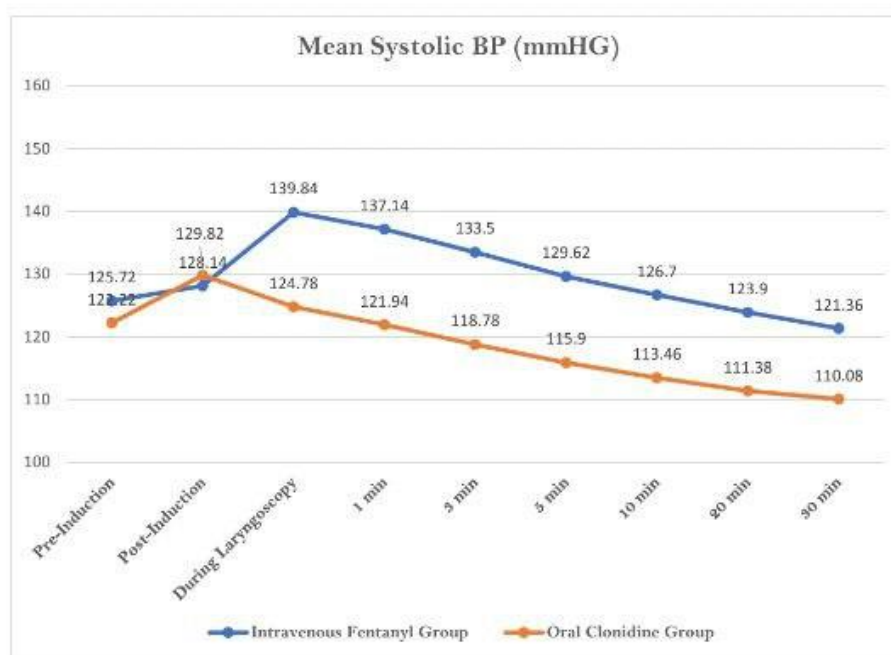
Time (Min.)	Intravenous Fentanyl Group n=50		Oral Clonidine Group n=50		P Value	Summary
	Mean	SD	Mean	SD		
Pre-Induction / Baseline	125.72	±9.22	122.22	±8.61	0.053	N.S
Post Induction / Pre- Laryngoscopy	128.14	±10.0	129.82	±10.03	0.404	N.S
During	139.84	±9.50	124.78	±8.25	0.001	Significant

Laryngoscopy						
1 min	137.14	±9.04	121.94	±7.86	0.001	Significant
3 min	133.50	±8.96	118.78	±7.67	0.001	Significant
5 min	129.62	±9.10	115.90	±7.50	0.001	Significant
10 min	126.70	±8.8	113.46	±7.18	0.001	Significant
20 min	123.90	±8.58	111.38	±7.08	0.001	Significant
30 min	121.36	±8.43	110.08	±5.89	0.001	Significant

\*N.S – Not Significant

The mean values of Baseline SBP in the groups Fentanyl and Clonidine were 125.72 and 122.22 respectively. The mean SBP Post-induction/Pre-laryngoscopy in the groups Fentanyl and Clonidine were 128.14 and 129.82 respectively.

The mean SBP during Laryngoscopy in the groups Fentanyl and Clonidine were 139.84 and 124.78 respectively and p value 0.001 is statistically significant. The mean SBP at 1 minute after intubation in the groups Fentanyl and Clonidine were 137.14 and 121.94 respectively and p value 0.001 is statistically significant. The mean SBP at 3 minutes after intubation in the groups Fentanyl and Clonidine were 133.50 and 118.78 respectively and p value 0.001 is statistically significant. The mean SBP at 30 minutes after intubation in the groups Fentanyl and Clonidine were 121.36 and 110.08 respectively and p value 0.001 is statistically significant.



**Chart 3: Trend chart showing Mean Systolic BP at various intervals in both the groups**

**Table no.4: Comparison of Diastolic Blood Pressure (mmHg) in two groups.**

Time (Min.)	Intravenous Fentanyl Group n=50		Oral Clonidine Group n=50		P Value	Summary
	Mean	SD	Mean	SD		
Pre-Induction / Baseline	79.54	±6.07	81.04	±6.26	0.227	N.S
Post Induction / Pre Laryngoscopy	80.66	±6.62	80.10	±6.05	0.660	N.S

During Laryngoscopy	91.18	±4.09	82.68	±6.15	0.001	Significant
1 min	88.36	±4.47	78.52	±5.59	0.001	Significant
3 min	85.58	±4.42	75.78	±5.46	0.001	Significant
5 min	82.36	±4.78	73.64	±5.34	0.001	Significant
10 min	80.32	±4.50	71.40	±4.52	0.001	Significant
20 min	78.46	±4.20	70.08	±4.21	0.001	Significant
30 min	76.22	±4.43	68.16	±3.75	0.001	Significant

\*N.S – Not Significant

The mean values of Baseline DBP in the groups Fentanyl and Clonidine were 79.54 and 81.04 respectively. The mean DBP Post-induction/Pre-laryngoscopy in the groups Fentanyl and Clonidine were 80.66 and 80.10 respectively and p value 0.660.

The mean DBP during Laryngoscopy in the groups Fentanyl and Clonidine were 91.18 and 82.68 respectively and p value 0.001 is statistically significant. The mean DBP at 1 minute after intubation in the groups Fentanyl and Clonidine were 88.36 and 78.52 respectively and p value 0.001 is statistically significant. The mean DBP at 3 minutes after intubation in the groups Fentanyl and Clonidine were 85.58 and 75.78 respectively and p value 0.001 is statistically significant. The mean DBP at 30 minutes after intubation in the groups Fentanyl and Clonidine were 76.22 and 68.16 respectively and p value 0.001 is statistically significant.

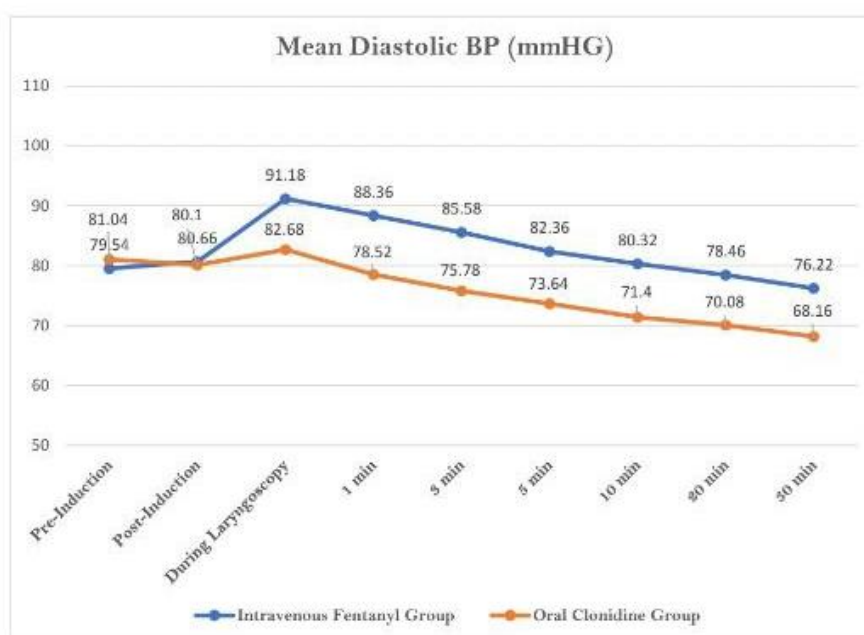


Chart 4: Trend chart showing mean Diastolic BP at various intervals in both the groups

Table no.5: Comparison of Mean Arterial Pressure (mmHg) in two groups.

Time (Min.)	Intravenous Fentanyl Group n=50		Oral Clonidine Group n=50		P Value	Summary
	Mean	SD	Mean	SD		
Pre-Induction / Baseline	94.90	±4.66	94.78	±5.38	0.905	N.S
Post Induction / Pre- Laryngoscopy	96.60	±4.49	98.52	±5.01	0.057	N.S

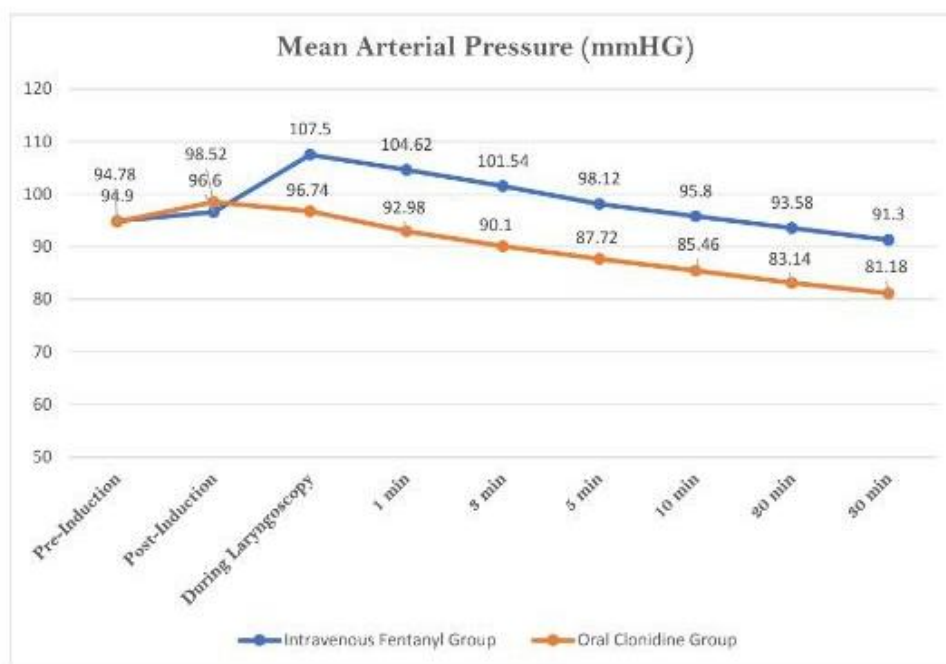


During Laryngoscopy	107.50	±3.88	96.74	±5.26	0.001	Significant
1 min	104.62	±5.00	92.98	±4.10	0.001	Significant
3 min	101.54	±4.99	90.10	±4.028	0.001	Significant
5 min	98.12	±4.28	87.72	±4.92	0.001	Significant
10 min	95.80	±4.08	85.46	±4.46	0.001	Significant
20 min	93.58	±3.89	83.14	±4.87	0.001	Significant
30 min	91.30	±3.92	81.18	±4.32	0.001	Significant

\*N.S – Not Significant

The mean values of Baseline MAP in the groups Fentanyl and Clonidine were 94.90 and 94.78 respectively. The mean MAP Post-induction/Pre-laryngoscopy in the groups Fentanyl and Clonidine were 96.60 and 98.52 respectively.

The mean MAP during Laryngoscopy in the groups Fentanyl and Clonidine were 107.50 and 96.74 respectively and p value 0.001 is statistically significant. The mean MAP at 1 minute after intubation in the groups Fentanyl and Clonidine were 101.54 and 92.98 respectively and p value 0.001 is statistically significant. The mean MAP at 3 minutes after intubation in the groups Fentanyl and Clonidine were 98.12 and 90.10 respectively and p value 0.001 is statistically significant. The mean MAP at 30 minutes after intubation in the groups Fentanyl and Clonidine were 91.30 and 81.18 respectively and p value 0.001 is statistically significant.



**Chart 5: Trend chart showing Mean Arterial Pressure at various intervals in both the Groups.**

### Discussion:

The endotracheal intubation and laryngoscopy were associated with a rise in the blood pressure, heart rate and the cardiac dysrhythmias. These above-mentioned effects may have serious repercussions on the high-risk patients like those with cardiovascular disease, increased intracranial pressure or anomalies of the cerebral vessels. Several drugs and techniques have been tried in an attempt to obtund the hyperactive sympathoadrenal pressor response to laryngoscopy and intubation.

In the present study we have compared the efficacy of: Oral Clonidine (5 micrograms per kilogram) and Intravenous Fentanyl (2 micrograms per kilogram) in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation. 100 patients were studied with each group comprising 50 patients. The patients in all the groups did not show any statistically significant differences in their age or gender distributions. We selected the optimal age range of 18 to 60 years. The anesthetic technique was chosen such that the drugs which were administered did not have any significant effects on the heart rate or the blood pressure. Both the groups were similarly premedicated regarding anxiolysis. At 0 min i.e., the pre- induction values of HR, SBP, DBP and MAP did not show any statistically significant difference in the two groups.

During the Pre-Laryngoscopy phase, the changes in Heart rate and blood pressure (systolic, diastolic, mean arterial pressure) were small and statistically insignificant when compared to the Baseline values in both the groups.

During Laryngoscopy and Intubation, the Heart rate increased in both the groups from their respective preoperative values (increased by 20% in Intravenous Fentanyl group, by 3% in Oral Clonidine group). This finding agreed with the study which was done by Smith and Derbyshire et al (1983) [3], who concluded that the plasma catecholamine concentration increased to the maximum at 1 minute after the laryngoscopy.

However, the clonidine group showed better attenuation of the HR as compared to the fentanyl group, which was statistically highly significant ( $P < 0.001$ ). Dipak and Malini (2014) [13] have also reported the effectiveness of clonidine in the attenuation of the haemodynamic response to laryngoscopy and endotracheal intubation.

During Laryngoscopy and Intubation, the blood pressure (systolic, diastolic and mean arterial pressure) increased in both the groups (mean arterial pressure increased by 12% in Intravenous Fentanyl group, 2% in Oral Clonidine group), however the clonidine group showed better attenuation of the SBP, DBP and MAP as compared to fentanyl Group, which was statistically highly significant ( $P < 0.001$ ).

In Oral Clonidine group, Heart Rate, SBP, DBP and MAP did not significantly rise following laryngoscopy and tracheal intubation. This finding was in accordance with the data which was available from other studies, such as that from the study which was conducted by H. Talebi in the patients in (2010) [14].

Our study showed a definite and a significant rise in the heart rate and the blood pressure in response to laryngoscopy and intubation. The clonidine premedicated patients showed a lower magnitude of the rise in the heart rate and the blood pressure. There was a statistically significant difference in the magnitude of the rise and the decline between the 2 groups. Both the Blood pressure response and the Heart rate were attenuated more effectively in the Oral clonidine group as compared to those in the Fentanyl group. Similar finding was seen in the study of Rukmini G., M. Srinivas Reddy (2019) [15] who concluded, that Oral Clonidine significantly attenuated the sympathetic response to laryngoscopy and intubation. IV Fentanyl also reduced the pressor response, but its effect was far lower than that of clonidine in attenuating the response.

Sameena K, Mahesh (2013)[16] did a similar study to compare IV Clonidine and IV Fentanyl and concluded that Clonidine significantly attenuated the pressor response compared to fentanyl.

During the 24 hours observation period, there were few patients with instances of side effects like nausea, vomiting, shivering. Other side effects like ventilatory depression, hypotension, hypertension, bradycardia or tachycardia were not seen in both the groups

### Conclusion:

Oral Clonidine 5 µg/kg proved to keep the hemodynamics in stable manner during laryngoscopy and endotracheal intubation and up to 30 mins post-intubation. Fentanyl in the dosage of 2 µg /kg given 5 minutes before laryngoscopy and intubation attenuated the hemodynamic changes, but was not equally effective in reducing the increase in heart rate and blood pressure. Clonidine in the dosage of 5 µg/kg given orally 90 minutes before intubation efficiently attenuated the haemodynamic changes to laryngoscopy and endotracheal intubation

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