

**To Compare Intravenous Dexmedetomidine, Clonidine and Fentanyl in Attenuating the Haemodynamic Response to Laryngoscopy and Endotracheal Intubation**

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**Conflicts of Interest:** Nil

**Abstract**

**Aims and objectives :** To compare the efficacy of iv Dexmedetomidine  $0.6\mu\text{gkg}^{-1}$ , iv Clonidine  $1\mu\text{gkg}^{-1}$  and iv Fentanyl  $2\mu\text{gkg}^{-1}$  for attenuating increase in HR, SBP,DBP and MAP during laryngoscopy and intubation under general anaesthesia and to study their side effects.

**Material &Methods :** Study was conducted in the Department of Anaesthesiology and Critical Care, Pt. B. D. Sharma, PGIMS, Rohtak in a prospective double-blind randomised manner. Hundred and fifty patients aged between 18 to 50 years belonging to ASA grade I,II were randomly divided into three groups , each group consists of 50 patients .Basal HR , SBP, DBP ,MAP ( $B_1$ ) were recorded. Group I(Dexmedetomidine group) received iv Dexmedetomidine  $0.6\mu\text{gkg}^{-1}$ ,group II (Clonidine group ) received iv Clonidine  $1.0\mu\text{gkg}^{-1}$ ,group III (Fentanyl group ) received iv Fentanyl  $2.0\mu\text{gkg}^{-1}$ . Study parameters were recorded ten minutes before intubation ( $B_2$ ), just before ( $T_0$ ) intubation and 1 minute ( $T_1$ ) , 3 minutes ( $T_3$ ) , 5 minutes ( $T_5$ ) after intubation.

**Results:** In our study, HR response to laryngoscopy and intubation was significantly attenuated by dexmedetomidine. However there was no attenuation with clonidine and fentanyl. SBP, DBP and MAP rise

following intubation was completely obtunded by dexmedetomidine as compared to clonidine and fentanyl.

**Conclusion:** Preoperative administration of a single dose of dexmedetomidine blunted the haemodynamic responses more than clonidine and fentanyl during laryngoscopy and intubation.

**Keywords:** Attenuation, Haemodynamic response, Laryngoscopy, Intubation, Dexmedetomidine, Clonidine, Fentanyl.

**Introduction**

Hypertension and tachycardia during intubation under general anaesthesia have been reported since 1950.<sup>1,2</sup> Increase in blood pressure and heart rate occurs most commonly from reflex sympathetic discharge in response to laryngotracheal stimulation, which in turn leads to increased plasma norepinephrine concentration.<sup>3</sup> These changes may be associated with morbidity and mortality in patients with heart disease and hypertension, provoking complications like bleeding, increased intracranial and intraocular pressure. There are various techniques by which this intubation-related stress response can be attenuated, all of which depend on reduction in input stimuli or the blockade of adrenergic responses e.g.deep anaesthesia, topical anaesthesia, use of ganglionic blockers, beta blockers<sup>4</sup>, antihypertensive agents like

phentolamine<sup>5</sup>, Sodium nitroprusside, nitroglycerine<sup>6</sup> and calcium channel blockers.<sup>7,8</sup>

$\alpha$ 2-Adrenergic agonists decrease sympathetic tone and preoperative use of clonidine has been shown to blunt the hemodynamic responses to noxious stimulation and to prevent the overall hemodynamic variability. It has also sedative and anesthetic sparing effects. Dexmedetomidine is a highly selective  $\alpha$ 2 receptor agonist having 8 times high affinity and  $\alpha$ 2 selectivity compared to clonidine and has a shorter duration of action than clonidine. It provides anesthetic sparing effects, anxiolysis, "cooperative sedation" and analgesia without respiratory depression. The mechanism of action of dexmedetomidine differs from clonidine as it possesses selective  $\alpha$ 2-adrenoceptor agonism, especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine.<sup>9,10</sup>

Fentanyl, an opioid analgesic, is popular as an intraoperative agent due to the cardiovascular stability provided by it, even in critically ill patients. Fentanyl has been used as premedication and its comparison has been done with other group of drugs to evaluate the attenuation of sympathetic response during laryngoscopy and intubation.<sup>11</sup>

### Aims & Objectives

The main objectives of the present study are:

1. To compare the efficacy of intravenous Dexmedetomidine  $0.6\mu\text{gkg}^{-1}$ , intravenous clonidine  $1\mu\text{gkg}^{-1}$  and intravenous fentanyl  $2\mu\text{gkg}^{-1}$  on changes in the heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean arterial blood pressure (MAP) during laryngoscopy and intubation under general anaesthesia.
2. To evaluate any side effects associated with the use of these drug.

### Methods

The present study was conducted in the Department of Anaesthesiology and Critical Care, Pt. B. D. Sharma, PGIMS, Rohtak in a prospective double-blind randomised manner. One hundred fifty patients belonging to American Society of Anesthesiologists (ASA) physical status I or II of either sex (18-50 years) presenting for general surgery under general anesthesia were included in the study. Patients were randomly divided into three groups, each group consists of 50 patients. Patients were kept fasting for 6 hours prior to the scheduled time of surgery. They were premedicated with a tablet of alprazolam 0.25 mg orally the night before surgery. On arrival in the operating room i.v line was secured and monitoring of NIBP, HR, ECG and SpO<sub>2</sub> was done by using Phillips Intellivue MP50 monitor. Basal HR, SBP, DBP, MAP (B<sub>1</sub>) were recorded.

Group I (Dexmedetomidine group, n=50) received iv dexmedetomidine  $0.6\mu\text{gkg}^{-1}$ .

Group II (Clonidine group, n=50) received iv clonidine  $1.0\mu\text{gkg}^{-1}$ .

Group III (Fentanyl group, n=50) received iv fentanyl  $2.0\mu\text{gkg}^{-1}$ .

After giving study drug haemodynamic parameters were recorded (B<sub>2</sub>) 10 minutes before induction. A uniform anesthetic technique were used in all three groups. All patients were preoxygenated for 3 minutes and induction was done with sleep dose of thiopentone sodium and vecuronium  $0.1\text{mgkg}^{-1}$  to facilitate laryngoscopy and intubation. All patients were manually ventilated for 3 minutes. Intubation was done with size 7mm ID (internal diameter) endotracheal tube (ETT) in female and 8mm ID ETT in male patients. Laryngoscopy and intubation was done by the trained observer in all the cases for consistency of observations. Study parameters were recorded just before (T<sub>0</sub>) intubation and 1 minute (T<sub>1</sub>), 3 minutes (T<sub>3</sub>), 5 minutes (T<sub>5</sub>) after intubation. Patients

were not disturbed till the study period was over. Thereafter, anesthesia was continued with nitrous oxide , oxygen , isoflurane and analgesics were administered based on the requirements. At the end of surgery, when patients having spontaneous respiratory attempts, residual neuromuscular blockade was reversed with inj. neostigmine and glycopyrrolate. Recovery was assessed and extubation was done after throat suction. After complete recovery patients were shifted to post anesthesia care unit, were observed for bradycardia, hypotension and sedation.

Data thus collected was compiled and analyzed using independent ‘t’ test (paired and unpaired) for quantitative data ; for non-quantitative data and association between groups with respect to various characteristics chi-square test was applied. A ‘p’ value of <0.05 considered significant, <0.001 highly significant and >0.05 was taken insignificant.

**Results**

All the groups were comparable in their age, gender, and body weight distribution. There was no significant intergroup difference from the baseline.

**Heart Rate**

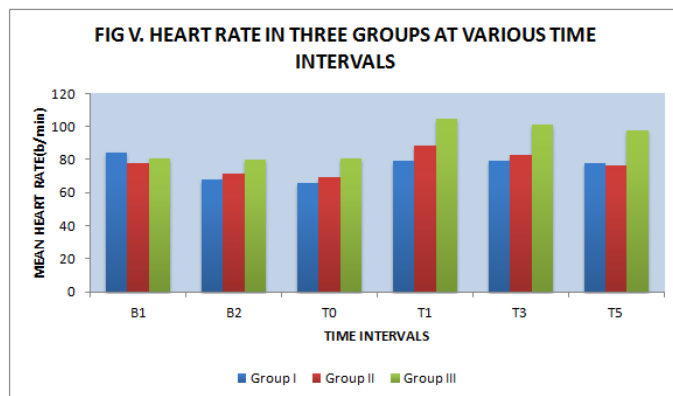
**Table-1:Heart rate in three groups at various time intervals (MEAN±SD).**

Groups	Baseline (B1)	Before induction (B2)	Just before Intubation (T0)	After intubation		
				1 min (T1)	3 min (T3)	5 min (T5)
Group I (Mean±SD)	84.36±10.43*	67.92±9.46	65.78±8.56	79.4±9.59*	79.2±9.80*	77.7±7.75*
Group II (Mean±SD)	77.76±8.94*	71.5±8.68	69.28±8.01	88.72±6.94*	82.7±6.50*	78.3±5.92*
Group III (Mean±SD)	80.76±10.12*	80.28±9.77	80.36±9.34	104.6±7.11*	101.1±6.31*	97.6±6.48*

# Base line heart rate of all patients of both groups are comparable to each other and there is no statistical difference between them (p > 0.05).

\*-The increase was highly significant in group F as compared to group D during laryngoscopy and after intubation (p <0.001 ).

Heart rate at various time intervals is shown in Fig.V.



**Comparison of heart rate in-between groups**

Before giving the drug the baseline heart rate(B1) in three groups was statistically comparable(p>0.05),(table-1).After giving dexmedetomidine just before induction(B2) there was significant fall in heart rate in group I,(p<0.05) as compared to group II,III. After induction just before intubation(T0) there was decrease in HR in all three groups which was more in group I. After intubation at 1 min(T1) there was rise in HR in all the groups which was highly significant in fentanyl group. At T3, there was fall in HR in group I whereas there was highly significant rise in HR in group II,III. But at T5 the fall in HR in group I was significantly high,as compared to group II,III where the HR was more than the baseline.

**Systolic Blood Pressure**

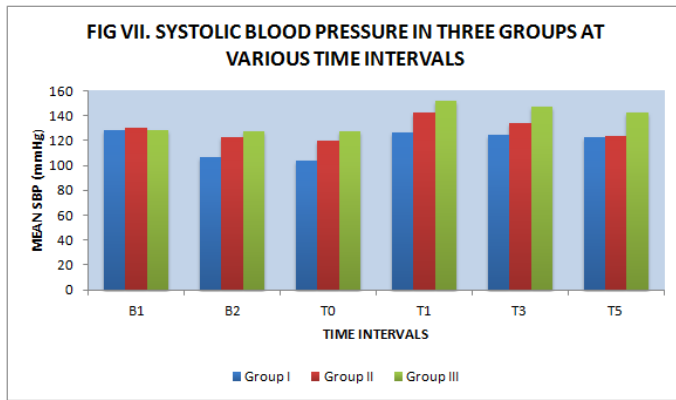
**TABLE-7: Systolic Blood pressure in three groups at various time intervals (MEAN±SD).**

Groups	Baseline (B1)	Before induction (B2)	Just before Intubation (T0)	After intubation		
				1 min (T1)	3 min (T3)	5 min (T5)
Group I (Mean±SD)	128.7±12.97#	107.0±12.01	103.4±9.58	126.9±12.24*	124.7±11.82*	122.7±11.87*
Group II (Mean±SD)	130.2±10.41#	122.4±11.30	119.5±11.66	142.6±8.03*	133.8±6.32*	132.7±16.77*
Group III (Mean±SD)	128.6±12.57#	127.8±11.90	127.3±11.93	152.2±6.13*	147.3±6.88*	142.2±7.82*

# - Base line systolic blood pressure of all patients of both groups are comparable to each other and there is no statistical difference between them (p> 0.05).

\*- The increase was highly significant in group F as compared to group D during laryngoscopy and after intubation (p<0.001).

Systolic blood pressure in three groups at various time intervals is depicted graphically in Fig.VI.



**Comparison of systolic blood pressure in-between groups**

Before giving the drug i.e baseline SBP was statistically comparable in all three groups( $p>0.05$ ),(table-4). After giving the drug i.e just before induction (B2) there was highest fall in group I, least in group III. After induction, just before intubation (T0) results were similar as that of B2. After intubation (T1) there was significant rise in SBP in group III, least in group I.

**Diastolic Blood Pressure**

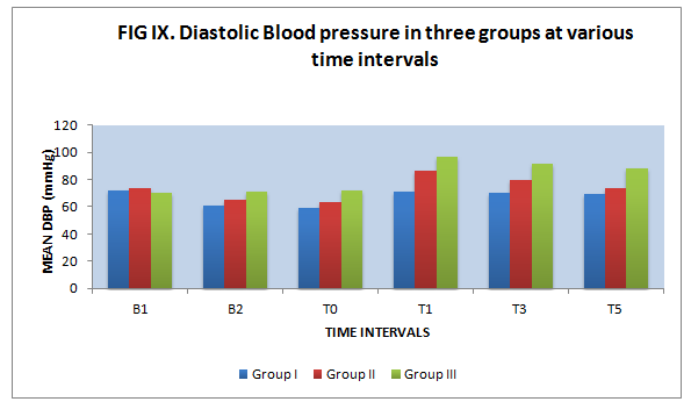
**TABLE 9: Diastolic Blood pressure in three groups at various time intervals (MEAN±SD).**

Groups	Baseline (B1)	Before induction (B2)	Just before Intubation (T0)	After intubation		
				1 min (T1)	3 min (T3)	5 min (T5)
Group I (Mean±SD)	72.3±8.38*	60.7±6.38	58.8±5.90	70.8±10.70*	70.2±10.05*	69.2±9.21*
Group II (Mean±SD)	73.2±6.95*	65.2±7.39	63.4±6.88	86.4±6.13*	79.9±5.23*	73.8±7.58*
Group III (Mean±SD)	70.4±8.46*	70.9±8.20	71.6±8.36	96.4±7.25*	91.4±8.26*	88.2±8.13*

# - Base line diastolic blood pressure of all patients of both groups are comparable to each other and there is no statistical difference between them ( $p > 0.05$ ).

\* - The increase was highly significant in group F as compared to group D during laryngoscopy and after intubation ( $p<0.001$ ).

Diastolic blood pressure in three groups has been shown in Fig.VII.



**Comparison of diastolic blood pressure in-between groups**

Before giving the drug i.e baseline DBP was statistically comparable in all three groups( $p>0.05$ ),(table-4). After giving the drug i.e just before induction (B2) there was highest fall in group I, least in group III. After induction, just before intubation (T0) results were similar as that of B2. After intubation(T1) there was significant rise in DBP in group III, least in group I.

**Mean Arterial Pressure**

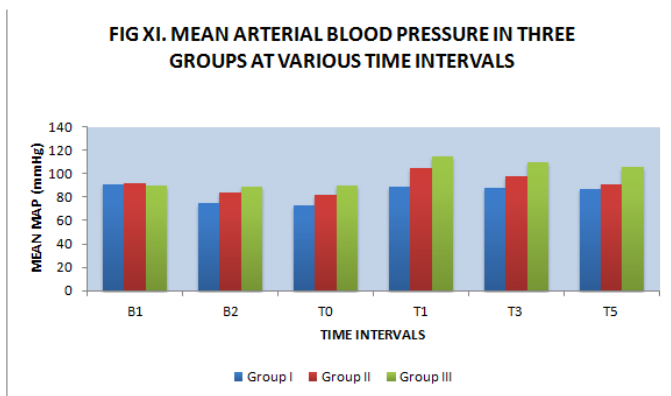
**TABLE-10: Mean arterial pressure in three groups at various time intervals (MEAN±SD).**

Groups	Baseline (B1)	Before induction (B2)	Just before Intubation (T0)	After intubation		
				1 min (T1)	3 min (T3)	5 min (T5)
Group I (Mean±SD)	90.6±8.97*	75.3±7.61	72.8±6.55	88.8±10.63*	87.5±10.10*	86.4±9.33*
Group II (Mean±SD)	91.9±6.24*	83.9±6.96	81.8±6.95	104.8±5.55*	97.5±4.96*	91.9±6.77*
Group III (Mean±SD)	89.6±8.68*	89.0±8.20	89.9±8.39	114.6±5.92*	109.5±7.01*	106.0±6.83*

# - Base line Mean Arterial Blood Pressure of all patients of both groups are comparable to each other and there is no statistical difference between them ( $p > 0.05$ ).

\* - The increase was highly significant in group F as compared to group D during laryngoscopy and after intubation ( $p<0.001$ ).

Mean arterial pressure in three groups at various time intervals is shown in Fig.VIII.



## Discussion

Haemodynamic changes associated with laryngoscopy and tracheal intubation in the form of tachycardia and hypertension, with or without arrhythmias were described by King BD et al in 1951.<sup>12</sup> It was interpreted to be due to reflex sympathoadrenal response. These nerves activate the suprasedgmental and hypothalamic sympathetic centres releasing catecholamines causing rise in arterial blood pressure and tachycardia. These changes are short-lived. But even this transient change in haemodynamics may lead to myocardial ischemia and subsequent myocardial infarction in susceptible individuals. This stress response can also lead to rise in intracranial and intraocular pressure, which can be hazardous in patients with open eye injuries, intracranial lesions and cerebro-vascular disease.

Fentanyl is an opioid analgesic. The principal actions of therapeutic value are analgesia and sedation. It acts as analgesic supplement to general and regional anaesthesia and in combination with a neuroleptic agent as an anaesthetic pre-medication for the induction of anaesthesia. Fentanyl brings haemodynamic stability during perioperative period by its action on cardiovascular and autonomic regulatory areas. It decreases sympathetic tone and increases parasympathetic tone. Fentanyl inhibits pituitary adrenal response directly or indirectly via hypothalamus.

Clonidine originally introduced as an antihypertensive drug, has analgesic, sedative and anxiolytic properties. It

improves the quality of induction, maintenance and recovery from anaesthesia. By its central sympatholytic action, it tends to attenuate the haemodynamic response to laryngoscopy and intubation and improve overall peri-anaesthetic cardiovascular stability.

Dexmedetomidine is highly selective alpha-2 agonist with analgesic, anxiolytic and sedative properties. It also exhibits cardio-protective, neuro-protective and reno-protective actions. It also has advantage of preservation of respiratory function. It causes hyperpolarization of noradrenergic neurons and suppression of neuronal firing in the locus coeruleus which leads to decreased systemic noradrenaline release, resulting in attenuation of sympathoadrenal response during laryngoscopy and tracheal intubation.

## Heart rate

In our study pretreatment with  $\alpha_2$ -adrenergic agonist dexmedetomidine  $0.6 \mu\text{gkg}^{-1}$  attenuated the heart rate response to laryngoscopy and tracheal intubation after induction of anaesthesia. Heart rate fell down significantly (19.27%) after giving dexmedetomidine which further decreased significantly (21.53%) after induction i.e just before intubation (T0) as compared to baseline ( $84.36 \pm 10.43$ ). After intubation at 1 min (T1) there was significant rise in heart rate (14.02%) as compared to B2 but remained below baseline level. The fall in heart rate compared to baseline (B1) was statistically significant ( $p < 0.05$ ) (Table-4,5; FIG. IV, V).

Our results were comparable to the results of study done by Sharma and Shankararayana, Sarkar et al and Rao et al.<sup>13,14,15</sup>

## Blood pressures

Dexmedetomidine  $0.6 \mu\text{gkg}^{-1}$  attenuated the pressor response to laryngoscopy and intubation. SBP(16.52%), DBP(15.45%) and MAP(16.55%) all decreased significantly after giving dexmedetomidine(B2) which further decreased by 19.23%, 18.08% and 19.32%

respectively after induction (T0) as compared to baseline(B1). After intubation at 1 min (T1) there was significant rise in blood pressures as compared to B2 but remained below baseline. The fall in blood pressures compared to baseline was statistically significant ( $p < 0.05$ ) (Table-4,8,9,10,11,12; FIG.IV,VIII,IX,X,XI,XII).

Our results were comparable to the results of study done by Sharma and Shankarnarayana, Sarkar et al and Mondal et al.<sup>13,14,16</sup>

### Thiopentone dose

Statistical evaluation between the groups showed a statistically highly significant reduction in dose of thiopentone sodium required for induction ( $p = 0.000$ ) i.e for group I ( $170.5 \pm 30.17$ ), group II ( $220 \pm 25.12$ ) and for group III ( $278 \pm 34.49$ ) mg respectively.

### Side effects

Three patients had bradycardia in dexmedetomidine group and three patients had hypotension in clonidine group which didn't need any treatment, while no side effects in fentanyl group. There were no episodes of any dysrhythmias and desaturation.

### Conclusions

Based on the present clinical comparative study, following observations were made:

1. Demographic profile of the patients i.e age, weight and sex distribution were comparable in all three groups.
2. Size of endotracheal tube and intubation time were also comparable in all three groups.
3. Baseline HR was comparable in all three groups.

HR decreased after giving dexmedetomidine (group I) and clonidine (group II) while it was maintained with fentanyl (group III). Following induction there was further decrease in HR in group I and group II. However, HR remained below baseline in group I even at 5 min following intubation whereas HR increased above baseline

in group II and III following intubation and persisted for 5 mins.

4. Baseline SBP, DBP and MAP were similar in all three groups.

After giving the drug and following induction significant fall in SBP, DBP and MAP was seen in group I and group II with minimal change in group III. SBP, DBP and MAP remained below the baseline in group I even at 5 min after intubation whereas rise in blood pressures was seen following intubation in group II and group III which persisted for 5 mins following intubation.

5. Bradycardia occurred in 6% of patients in group I and hypotension in 6% of patients in group II.
6. There were no episodes of dysrhythmias or desaturation in any of the patients in all three groups.
7. Mean thiopentone dose required for induction was less in group I compared to group II and group III.

After studying various factors we conclude that dexmedetomidine  $0.6 \mu\text{gkg}^{-1}$  i.v. over 10 mins before induction attenuates HR response to laryngoscopy and intubation. However there was no attenuation with clonidine and fentanyl and SBP, DBP and MAP rise following intubation was also completely obtunded by dexmedetomidine as compared to clonidine and fentanyl. Side effects were seen with dexmedetomidine and clonidine which were managed adequately. Thiopentone requirement was much less in dexmedetomidine group compared to clonidine and fentanyl group.

Hence, dexmedetomidine  $0.6 \mu\text{gkg}^{-1}$  i.v. significantly attenuates heart rate and blood pressure response following laryngoscopy and intubation as compared to clonidine  $1 \mu\text{gkg}^{-1}$  i.v. and fentanyl  $2 \mu\text{gkg}^{-1}$  i.v.

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