

## Comparative Study of Intravenous Clonidine and Dexmedetomidine for Blunting Pressor Response during Endotracheal Intubation

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### Abstract

### Original Research Article

**Background and Aims:** Laryngoscopy and tracheal intubation stimulates the sympathetic nervous system. Dexmedetomidine has an affinity for alpha2 receptors 8 times greater than that of clonidine. The study aimed to compare the effects of intravenous (IV) dexmedetomidine and clonidine on the pressor response among patients undergoing tracheal intubation in elective surgeries under general anaesthesia. **Methods:** After ethical clearance, this randomised double blinded study including 116 patients, aged between 18 to 55 years, belonging to American Society of Anesthesiologist (ASA) classes I and II scheduled for elective surgeries under general anaesthesia were randomly allocated into Groups A (n=58) and B(n=57). Group A received dexmedetomidine 0.5mcg/kg and Group B received clonidine 3mcg/kg, both diluted in 0.9% 100 ml saline and were infused over a period of 10 minutes. Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP) were recorded before administration of the drugs, after induction, immediately after intubation and 2, 4, 6, 8 and 10 minutes after intubation. Adverse effects if any were noted. **Results:** Demographic characteristics in both the groups were comparable. Mean of SBP (Group A 124±14.70 vs Group B 135±24.66mmHg, p=0.003), DBP (Group A 84.02±11.71 vs Group B 9.63±17.09mmHg, p=0.042), MAP (Group A 97.34±12.75 vs Group B 104.68±18.98mmHg, p=0.016) and HR (Group A 79.95±10.22 vs Group B 85.07±16.06bpm, p=0.043) immediately after intubation was lower in Group A. **Conclusion:** Dexmedetomidine 0.5mcg/kg infusion over 10 minutes before induction blunts haemodynamic response to laryngoscopy and intubation more effectively than clonidine 3mcg/kg without any significant adverse effect.

**Keywords:** Dexmedetomidine, clonidine, laryngoscopy, intubation, randomised control trial.

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## INTRODUCTION

Laryngoscopy and intubation stimulates the patients airway causing intense reflex sympathetic activity which often causes tachycardia, hypertension and dysrhythmia. These effects may further be associated with hypoxia, hypercapnia or cough [1-3]. The extent of haemodynamic responses, which occurs due to increase in plasma nor epinephrine concentration, is proportional to the degree of manipulations of oropharyngeal structures [4, 5]. Lifting the base of the tongue and epiglottis by laryngoscope blade and stimulation of the trachea during intubation are thought to be the causes. These lead to activation of sympathoadrenal axis that is manifested by catecholamine rise [6]. It may lead to complications, particularly in patients with history of hypertension, coronary artery disease, intracranial aneurysm and recent myocardial infarction. Alpha

agonist have special places in anaesthesia in the aspect of controlling the post intubation haemodynamic response. Dexmedetomidine and clonidine are two pharmacologically related alpha agonists [7]. Dexmedetomidine has an affinity for alpha 2 receptors 8 times greater than that of clonidine making it a complete alpha2 agonist. It diminishes norepinephrine release and inhibits sympathetic activity [8]. The inhibition of sympathetic activity causes decreased heart rate and blood pressure.

## AIMS

The primary aim of this study is to compare the effects of single dose of intravenous infusion of dexmedetomidine and clonidine as pre medication on the haemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing elective surgeries under general anaesthesia.

## MATERIALS AND METHODS

The present randomised clinical trial was carried out following approval of the study protocol on the 30<sup>th</sup> July, 2018 by the Institutional Ethics Committee (No. MC/190/2007/Pt-1/IEC/99) under the department of Anaesthesiology and Critical Care in Gauhati Medical College and Hospital in a period of one year from July 1, 2018 to 30 June, 2019. A total of 116 patients, aged between 18 to 55 years, with mallampati score 1 and 2, belonging to ASA I and II scheduled for elective surgeries under general anaesthesia were randomly allocated into two groups.

### INCLUSION CRITERIA

1. Adult patients of either sex aged between 18 to 55 years.
2. Patients belonging ASA -1 and ASA -2 physical status.
3. Patients who are scheduled for elective surgery under GA.
4. Patients with Mallampatti score of 1 and 2.

### EXCLUSION CRITERIA

1. Patients with coronary artery disease.
2. Patients with Ischemic heart disease.
3. Patients with chronic obstructive pulmonary disease.
4. Patients with chronic renal disease.
5. Patients with known arrhythmia.
6. Diagnosed case of hypertension or blood pressure more than 140/90 on examination.

### DEMOGRAPHIC CHARACTERISTICS

**Table-1: Table showing gender distribution in the groups**

		Group_A No (%)	Group_B No (%)	Total No (%)	Chi	Sig.
Gender	Male	13 (22.4%)	15 (26.3%)	28 (24.3%)	0.238	0.669
	Female	45 (77.6%)	42 (73.7%)	87 (75.7%)		
	Total	58 (100%)	57 (100%)	115 (100%)		

No- Absolute number, %-percentage

The two groups were similar in gender distribution and comparable. The two groups were homogeneous with respect to age distribution ( $p=0.753$ ), ASA grade distribution ( $p=0.541$ ), weight distribution ( $p=0.546$ ), height distribution ( $p=0.323$ ), diagnosis wise distribution ( $p=0.163$ ) and with respect to surgery performed ( $p=0.268$ ). The two groups were comparable with respect to Mallampatti score of both the groups ( $p=0.569$ ).

7. Patients with BMI less than 18 and more than 25.
8. Patients with restricted neck movements.
9. Patients with autonomic neuropathy, diabetes Mellitus.
10. Patient who refuse to take part in the study.
11. Cases where laryngoscopy and intubation has taken more than 30 seconds.

The baseline systolic BP, Diastolic BP, Mean Arterial Pressure, Heart rate and peripharel oxygen saturation were measured. Group A ( $n=58$ ) received dexmedetomidine  $0.5\mu\text{g}/\text{kg}$  and Group B ( $n=57$ ) received clonidine  $3\mu\text{g}/\text{kg}$ , both diluted in 0.9% 100ml saline and were infused over a period of 10 minutes before induction. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP) were recorded before administration of the drugs, after induction, immediately after intubation and 2,4,6,8 and 10 minutes after intubation. Adverse effects, if any, were noted.

## RESULTS

A total of 115 patients of either sex posted for elective surgery under GA at GAUHATI MEDICAL COLLEGE AND HOSPITAL under department of ANAESTHESIOLOGY AND CRITICAL CARE were analysed for this randomised control study with 58 patients in Group A –dexmedetomidine group and 57 patients in Group B – clonidine group.

### HAEMODYNAMIC VARIABLES

The mean baseline systolic blood pressure are similar in both the groups, statistical difference being insignificant ( $P=0.929$ ). After the administration of the trial drug over 10 minutes (end of infusion), the mean systolic blood pressure decreased in the group A at all the intervals and the decrease was statistically significant. In group B also the mean systolic blood pressure decreased at all intervals except immediately after intubation. The mean systolic blood pressure decreased in all other intervals in group B which was statistically significant. Inter group comparison shows

the decrease in mean systolic blood pressure to be significantly more in Gr -A than Gr-B at after intubation (ie T3), and after 2min, 4 min, 6min, 8 min and 10 minutes of intubation with p value < 0.05. This study found that there is statistically significant difference in mean SBP towards T3 among group A (124.43 ± 14.702) and Group B (135.93 ± 24.663) participants, t (113)=-3.043 ,p=0.003 at 95% confidence interval. After laryngoscopy and intubation, mean systolic blood pressure increased in group B, with increase of 5.61 mmHg (4.30%) with p value 0.0399. In case of Group A after laryngoscopy and intubation, mean systolic blood pressure decreased, with decrease of 6.04 mmHg (4.63%) with p value =0.0036 . Inter group comparison shows the increase in systolic blood pressure to be higher in group-B in comparison to group-A (p value = 0.003) which is statistically

significant. At 2 min after intubation in Group A (dexmedetomidine) mean SBP decreased by 13.93% (p value <0.0001). At 2 min after intubation in Group B mean SBP decreased by 7.87% from baseline (p value<0.05). On intergroup comparison however, mean SBP was significantly higher in Group B (clonidine group) as compared to Group A (dexmedetomidine) with p value =0.009. In 4 min, 6 min, 8 min and 10 minutes after intubation mean SBP in group A remained significantly lower than baseline. Again also in group B in 4 min, 6 min, 8 min and 10 minutes after intubation mean SBP remained significantly lower than baseline (p value<0.05) .However on inter group comparison, the mean SBP of group B was significantly higher as compared to group A in 4 mins, 6 mins, 8 mins and 10 mins after intubation.

**Table-2: Inter Group Comparison of Mean Systolic Blood Pressure (MEAN SBP)**

intervals	Group	N	Mean(mmHg)	Std. Deviation(m mHg)	Independent Samples Test			
					t	df	Sig. (2-tailed)	Mean Difference
T0 SBP	Group A	58	130.47	9.283	0.089	113	0.929	0.15
	Group B	57	130.32	8.737				
T1 SBP	Group A	58	118.26	11.615	0.256	113	0.798	0.557
	Group B	57	117.70	11.686				
T2 SBP	Group A	58	104.14	12.601	-0.265	113	0.792	-0.599
	Group B	57	104.74	11.62				
T3 SBP	Group A	58	124.43	14.702	-3.043	113	0.003	-11.499
	Group B	57	135.93	24.663				
T4 SBP	Group A	58	112.29	13.761	-2.654	113	0.009	-7.777
	Group B	57	120.07	17.473				
T5 SBP	Group A	58	104.48	10.626	-2.435	113	0.016	-6.71
	Group B	57	111.19	18.04				
T6 SBP	Group A	58	101.97	8.641	-3.065	113	0.003	-7.245
	Group B	57	109.21	15.752				
T7 SBP	Group A	58	102.72	9.702	-3.648	113	0.000	-8.767
	Group B	57	111.49	15.464				
T8 SBP	Group A	58	105.26	11.14	-3.456	113	0.001	-8.548
	Group B	57	113.81	15.123				

mmHg- millimetre of mercury]

After the 10 minutes of trial drug infusion, mean diastolic blood pressure decreased from their baseline in all intervals in Group A (dexmedetomidine group) except at after intubation (ie T3). The decrease

of DBP from baseline is statistically significant in all intervals except at after intubation in Group A(p<0.05) .In group B also, mean diastolic pressure decreased from their baseline after the 10 minutes of trial drug

infusion in all intervals except at after intubation (ie T3). The decrease in mean DBP from baseline is significant in Group B except at immediately after intubation (T3) with  $p < 0.05$ . Maximum decrease in mean DBP in group A was observed at 6 minutes after intubation (ie T6) with 16.55 mmHg (19.77%). Maximum decrease in mean DBP in Group B was observed at after induction (ie T2) with 14.98 mmHg (17.93%) Intergroup comparison shows that the decrease of mean DBP was significantly more in Group

A in comparison to group B at immediately after intubation (ie T3), 4 minutes after intubation (ie T5), 6 mins (ie T6), 8 minutes (T7) and 10 minutes after intubation (T8). Mean diastolic blood pressure increased in both the groups on laryngoscopy and intubation, with 0.3 mmHg (0.36%) in group-A and 6.09 mmHg (7.29%) in group-B. However, this rise in mean diastolic blood pressure in Group B was significantly higher when compared to Group A with  $p$  value = 0.042.

**Table-3: Inter Group Comparison of Mean Diastolic Blood Pressure (MEAN DBP)**

intervals	Group	N	Mean(mmHg)	Std. Deviation(mmHg)	Independent Samples Test			
					t	df	Sig. (2-tailed)	Mean Difference
T0 DBP	Group A	58	83.72	7.764	0.14	113	0.889	0.18
	Group B	57	83.54	5.85				
T1 DBP	Group A	58	77.59	8.978	1.097	113	0.275	1.744
	Group B	57	75.84	8.04				
T2 DBP	Group A	58	67.24	10.323	-0.663	113	0.508	-1.32
	Group B	57	68.56	11.007				
T3 DBP	Group A	58	84.02	11.714	-2.058	113	0.042	-5.614
	Group B	57	89.63	17.095				
T4 DBP	Group A	58	74.62	11.043	-1.236	113	0.219	-2.976
	Group B	57	77.6	14.569				
T5 DBP	Group A	58	67.52	10.143	-2.282	113	0.024	-4.956
	Group B	57	72.47	12.995				
T6 DBP	Group A	58	67.17	8.013	-2.439	113	0.016	-4.442
	Group B	57	71.61	11.269				
T7 DBP	Group A	58	68.79	8.113	-3.386	113	0.001	-6.628
	Group B	57	75.42	12.463				
T8 DBP	Group A	58	72.21	8.803	-2.923	113	0.004	-6.021
	Group B	57	78.23	12.931				

mmHg- millimetre of mercury

After completion of trial drug infusion over 10 minutes, mean MAP decreased from baseline in the groups A at all intervals. The decrease being maximum at after induction (T2) with 21.52 mmHg (21.53%). In Group B after completion of trial drug infusion over 10 minutes, mean MAP decreased from baseline in all intervals except immediately after intubation (ie T3). The decrease being maximum at after induction (T2) with 19.52 mmHg (19.52%). Intergroup comparison shows the decrease in mean MAP to be significantly more in group-A in comparison to group-B at both after intubation (ie T3) and 2 minutes after intubation (ie T4) ( $p=0.016$  at after intubation and  $p=0.049$  at 2 min after intubation). At laryngoscopy and intubation, mean

MAP decreased from baseline in the group A with decrease of 2.59 mmHg (2.59%). While in group B, the mean MAP after laryngoscopy and intubation increased from baseline with an increase of 4.72 mmHg (4.72%). The intergroup comparison shows at after intubation decrease in mean MAP to be significantly more in Group A in comparison to group B,  $p$  value=0.016. It was observed that the mean MAP after 4 minutes, 6 minutes, 8 minutes, 10 minutes after intubation decreased from baseline in both the groups and the decrease has been significant. On intergroup comparison it was found that decrease of mean MAP in group A was higher than group B at all these intervals but the difference is not statistically significant.

**Table-4: Inter Group Comparison of Mean Map between Group A and Group B**

	Group	N	Mean(mmHg)	Std. Deviation(mmHg)	Independent Samples Test			
					t	df	Sig. (2-tailed)	Mean Difference
T0 MAP	Group A	58	99.93	9.134	-0.022	113	0.983	-0.034
	Group B	57	99.96	7.443				
T1 MAP	Group A	58	90.67	11.036	0.495	113	0.621	0.936
	Group B	57	89.74	9.11				
T2 MAP	Group A	58	78.41	11.716	-0.945	113	0.347	-2.025
	Group B	57	80.44	11.263				
T3 MAP	Group A	58	97.34	12.759	-2.437	113	0.016	-7.339
	Group B	57	104.68	18.98				
T4 MAP	Group A	58	85.78	11.977	-1.774	113	0.049	-4.663
	Group B	57	91.44	15.967				
T5 MAP	Group A	58	81.67	9.811	-0.171	113	0.320	-2.841
	Group B	57	84.51	13.782				
T6 MAP	Group A	58	81.43	8.129	-1.112	113	0.059	-2.234
	Group B	57	83.67	11.695				
T7 MAP	Group A	58	85.39	8.78	-1.94	113	0.076	-2.142
	Group B	57	87.53	13.611				
T8 MAP	Group A	58	87.79	8.671	-2.487	113	0.051	-2.393
	Group B	57	90.18	13.545				

mmHg-millimetre of mercury

After completion of trial drug infusion over 10 minutes, mean heart rate decreased in comparison to baseline in group A at all the intervals except after 6 minutes and 8 minutes after intubation (ie T6 and T7). While in group B, the mean heart rate decreased from baseline at after completion of trial drug infusion over 10 minutes (i.e T1) and after induction (T2).

However, in group A, the decrease of mean HR from baseline was statistically significant ( P value <0.05) at after completion of trial drug infusion over 10 minutes (T1), after induction(T2) and after 10 minutes of intubation(T8). Also in group B, the decrease in mean heart rate from baseline was statistically significant after completion of the infusion of the trial drug over 10 minutes (T1), p value=0.02. In group A, maximum decrease of mean heart rate occurred at after completion of infusion of the trial drug over 10 minutes (T1) with 8.99 mmHg (10.27%) decrease from baseline. In group B maximum decrease of mean heart rate from baseline was observed at after induction (i.e T2) with 3.49 mmHg (4.19%).

In the inter group comparison shown in table 1.20, the decrease in mean heart rate in group-A, is statistically significant (P< 0.05) immediately after intubation (T3), 2 minutes (T4) and 4 minutes after intubation (T5) in comparison to group-B.

Immediately after laryngoscopy and intubation, mean heart rate decreased from baseline in group A while it increased in group B. There was 7.57bpm (8.64%) decrease from baseline in group-A, which is not significant (p value=0.1003). In group- B, increase of mean hear rate was 1.86 bpm (2.23%) from

baseline which is statistically significant (p value <0.0001).

However, inter group comparison shows the increase in mean heart rate at laryngoscopy and intubation to be significantly more in group-B compared to group A (p value=0.043). At 2 min after intubation, the heart rate decreased from baseline by 6.76 % in group-A (p>0.05, not significant) and it is increased from baseline 1.92% in group- B (p value=0.008, significant).

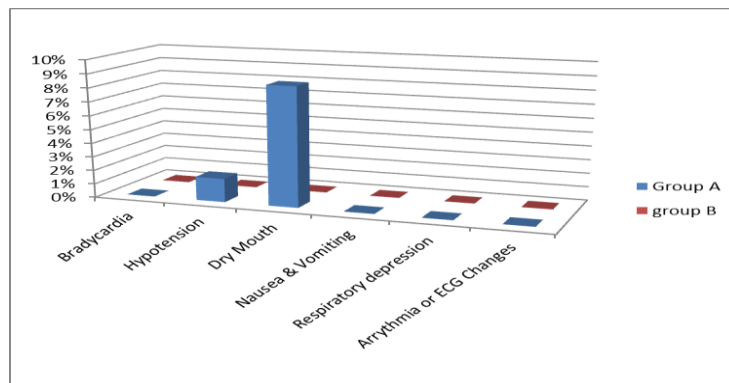
On observation at 2 minutes(T4) and 4 minutes (T5) after intubation, the mean heart rate was significantly high in group-B (Clonidine) compared to group-A (dexmedetomidine), p value being 0.024 at T4 and 0.003 at T5 respectively.

At 6 minutes (T6), 8 minutes (T7) and after intubation, the mean heart rate was higher in group A from the baseline, and significant with p value being <0.0001 at T6 and <0.05 at T7. While in group B, at 6 minutes and 8 minutes after intubation, the mean heart rate was higher from the baseline, but not statistically significant. On inter group comparison, at 6 minutes and 8 minutes after intubation ,the mean heart rate was found to be higher in group B ,but the difference is not significant (p value<0.05). At 10 minutes after intubation (i.e T8), the mean heart rate in Group A was 4.5% lower from baseline while in Group B it was 0.58% higher from baseline. On inter group comparison at 10 minutes after intubation (T8), the mean heart rate was higher in group B compared to group A, but the difference is not statistically significant with p value being 0.145.

**Table-5: Intergroup Comparison of Mean Heart Rate (HR) Between Group A and Group B**

	Group	N	Mean(mmHg)	Std. Deviation(mmHg)	Independent Samples Test			
					t	df	Sig.(2tailed)	Mean Difference
T0 HR	Group A	58	87.52	14.789	1.487	113	0.140	4.307
	Group B	57	83.21	16.257				
T1 HR	Group A	58	78.53	14.805	0.665	113	0.508	-1.957
	Group B	57	80.49	16.715				
T2 HR	Group A	58	78.55	15.475	0.413	113	0.680	-1.168
	Group B	57	79.72	14.822				
T3 HR	Group A	58	79.95	10.225	2.044	113	<b>0.043</b>	-5.122
	Group B	57	85.07	16.06				
T4 HR	Group A	58	81.60	11.816	2.524	113	<b>0.024</b>	-3.204
	Group B	57	84.81	15.979				
T5 HR	Group A	58	79.16	10.917	3.067	113	<b>0.003</b>	-7.950
	Group B	57	87.11	16.386				
T6 HR	Group A	58	91.45	14.75	0.673	113	0.502	-1.920
	Group B	57	93.37	15.845				
T7 HR	Group A	58	87.78	13.107	0.365	113	0.716	-0.979
	Group B	57	88.75	15.567				
T8 HR	Group A	58	83.55	11.691	0.058	112	0.954	-0.145
	Group_B	56	83.70	14.942				

mmHg-millimetre of mercury



**Fig-1: Showing adverse effects of both the groups**

It can be seen from the above table that dry mouth is a side effect of dexmedetomidine group. Hypotension in 1 patient in dexmedetomidine group was managed by fluid bolus of 200ml.

**DISCUSSION**  
**CHANGES IN THE HAEMODYNAMIC PARAMETERS PRE-LARYNGOSCOPY PERIOD**

In the present study after giving the trial drugs, there was fall of systolic B.P, diastolic B.P, heart rate and MAP from the baseline values in both groups.

During the pre-laryngoscopy period, it was observed that the maximum fall in SBP, DBP and MAP was at induction of anaesthesia (T2) in both the groups. In group A mean fall of SBP was 20.18%, mean DBP decrease was 19.68% and mean MAP decrease was 21.53% from the baseline values. Similarly, in group B, the mean fall of SBP was 19.63%, mean DBP decrease was 17.93% and the mean MAP decrease was 19.52%. Although, it was observed that the fall in mean SBP, DBP, MAP was more in dexmedetomidine group than the clonidine group but it was not significant.

During the pre-laryngoscopy period, there was also reduction in the mean heart rate in both the groups after the trial drug administration. The reduction of heart rate was maximum at the end of drug infusion in dexmedetomidine group with a decrease of 10.27% from baseline and in clonidine group the reduction in heart rate was maximum after induction with a decrease of 4.19% from baseline. Although the reduction was more in dexmedetomidine group but it was not significant. The initial reduction in blood pressure and heart rate in both groups could be due to the central sympatholytic and also anxiolytic effect.

Aantaa R *et al.*, [10] in another placebo-controlled study, evaluated the effects of single dose 0.5microgram/kg i.v dexmedetomidine, on thiopental anaesthetic requirements and the haemodynamics. They found that a 10% decrease in systolic blood pressure and 9% decrease in diastolic blood pressure after dexmedetomidine infusion. The difference in degree of change in blood pressure from our study could be due to difference in the rate of infusion of the study drugs. They infused dexmedetomidine over 60 seconds whereas we infused the drug slowly over 10 minute. Again, they used thiopentone as an induction agent while we in our study used propofol for induction. The initial reduction in blood pressure and heart rate in the dexmedetomidine group (Group A) in our study correlates well with the placebo controlled study done by Sarkar *et al.*, [9]. They studied the effects of 0.5 microgram/kg dexmedetomidine and 3 microgram /kg clonidine on haemodynamic response and found that mean SBP, DBP and MAP in the dexmedetomidine group were lower than in clonidine group in pre laryngoscopy period although the difference being not statistically significant.

#### AFTER LARYNGOSCOPY AND INTUBATION

In our study we noticed that mean diastolic blood pressure increased immediately after laryngoscopy and intubation (T3) in clonidine groups. However in dexmedetomidine group the increase of mean DBP from baseline immediately after intubation was 0.36% which is insignificant while in clonidine group there was significant increase of 7.29%. Also, in the dexmedetomidine group, the mean systolic blood pressure immediately after laryngoscopy and intubation decreased from baseline by 4.63%, while it increased by 4.30% in the clonidine group.

Similarly, in the dexmedetomidine group mean arterial pressure immediately after laryngoscopy and intubation decreased from baseline by 2.59% while in clonidine group it increased from baseline by 4.72%. In the dexmedetomidine group mean heart rate immediately after laryngoscopy and intubation also decreased from baseline by 8.64% while in clonidine group the mean heart rate increased from baseline by 2.23%.

These findings of dexmedetomidine and clonidine on SBP, DBP, MAP and HR on laryngoscopy and intubation in our study correlate well with that of Sarkar *et al.*, [9]. They also studied the effects of 0.5 microgram/kg dexmedetomidine and 3 microgram/kg clonidine on haemodynamic response to tracheal intubation. They found in the clonidine group there had been a steep increase in all the haemodynamic parameters i.e SBP, DBP, MAP and HR, from baseline, between induction to intubation. However no such change was observed in the dexmedetomidine group. In our study, on intergroup comparison we found that in clonidine group mean SBP, DBP, MAP and HR were significantly higher than dexmedetomidine group immediately after laryngoscopy and intubation.

Therefore, we have seen that a single dose of 0.5 microgram/kg body weight of dexmedetomidine given as infusion over 10 minutes before induction of anaesthesia obtunded the haemodynamic response to laryngoscopy and intubation more effectively in comparison to 3 microgram/kg body weight of clonidine.

## CONCLUSION

We conclude that:

1. Intravenous dexmedetomidine given in a dose of 0.5 microgram/kg body weight before induction helps attenuate the stress response to laryngoscopy and intubation.
2. In comparison to clonidine 3 microgram/kg given intravenously as preanaesthetic dose in a similar fashion, dexmedetomidine 0.5 microgram/kg body weight provides better haemodynamic stability in response to laryngoscopy and intubation.
3. In a dose of 0.5 microgram/kg given slow i.v, adverse effects like hypotension and bradycardia can be avoided.
4. Dryness of mouth is a common side effect of dexmedetomidine.

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