

## Comparison of dexmedetomidine versus esmolol (Intravenously) in reduction of cardiovascular responses to intubation during induction of general anesthesia- A randomised clinical trial

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### Abstract

**Introduction and Aim:** The cardiovascular changes to airway manipulation like tachycardia and hypertension occur secondary to catecholamine secretion. These changes make less effects on normal patients but can be hazardous in cardiac compromised patients. Various pharmacological measures are tried to lessen these ill effects. As a result we made an effort to compare the usefulness of two drugs, highly specific  $\alpha_2$  agonist Dexmedetomidine at a dosage of  $1\mu\text{g}/\text{kg}$  versus Esmolol  $1\text{mg}/\text{kg}$ ; in reducing these effects during induction of G.A.

**Materials and Methods:** In this randomized clinical trial 102 patients, of age group 18-65 years and American Society of Anesthesiology classification I/ II, undergoing various surgeries under G.A. requiring intubation were distributed into 2 groups of 51 patients each. Group D patients were given Dexmedetomidine  $1\mu\text{g}/\text{kg}$  in diluted form over a time period of 10 minutes and Group E patients were given Esmolol  $1\text{mg}/\text{kg}$  diluted to 10 ml and given over 1 min. Induction of anesthesia was done with volatile agent sevoflurane. Maintenance was done with O<sub>2</sub> and N<sub>2</sub>O 30:60 along with vecuronium. Monitoring was done and hemodynamic parameters were recorded at particular intervals during laryngoscopy and intubation of trachea.

**Results:** All observations were expressed as mean and standard deviation. Based on statistical analysis the Baseline heart rate, and baseline mean arterial pressure were comparable in both the groups. The decrease in mean HR observed at, 3, 5 and 10 minutes after intubation in Group D was statistically highly significant compared to mean HR in group E ( $p < 0.000$ ). (table 2). The mean fall in SBP in group D at 1, 3, 5 and 10 minutes after intubation was statistically highly significant ( $p = 0.000$ ) compared to the Esmolol group E. The fall in mean DBP value at 1, 3, 5 and 10 minutes of intubation were statistically highly significant ( $p = 0.000$ ) in group D compared to the latter group. The mean basal MAP, 2min after drug administration and 1min after induction are comparable in both groups ( $p > 0.05$ ). The fall in mean MAP values in group D at 1, 3, 5 and 10 minutes of intubation were statistically highly significant ( $p < 0.0000001$ ) compared to group E. 1min after induction fall in mean RPP value in D group is statistically higher than in E Group ( $P = 0.0243$ ). We also noticed hypotension in 5 patients and a fall in heart rate in 3 patients of study group in group D which did not need any medication. However no patients in the latter group had these side effects, we attribute this to the lesser dosage of esmolol used.

**Conclusion:** This study shows that dexmedetomidine  $1\mu\text{g}/\text{kg}$  is better than esmolol  $1\text{mg}/\text{kg}$  for lessening the stress response to airway manipulation

**Keywords:** Dexmedetomidine, Endotracheal intubation, Esmolol Laryngoscopy, Hemodynamic responses.

### Introduction

Pressure response to laryngoscopy and intubation is a well-known factor which may present in various forms, for instance autonomic disturbance, increase in ocular and cranial pressure thereby causing tachycardia, hypertension, arrhythmias etc.<sup>1</sup> These fluctuations are found to be due to sympathetic stimulation<sup>2</sup> secondary to increased catecholamine activity.<sup>3</sup> Various factors are found to increase the intensity of these changes such as time taken for laryngoscopy, insertion of orotracheal tube, the variety of blade<sup>4</sup> the agent used to anesthetize and the adequacy of anesthesia. These changes are maximum at one minute after intubation and persist for ten minutes. Although well tolerated by normal healthy patients, it may result in hazards like myocardial ischemia, sudden failure of left ventricular chamber of heart, dysrhythmias, pulmonary edema and CVA in individuals in whom multiple organs are suffering from

severe congestion due to fluid that is inadequately circulated by the failing heart.<sup>5,7</sup> {end organ decompensation}. An increase in pulse rate together with elevation in systolic BP increases the rate pressure product, thus compromising myocardial contractility and oxygen supply.<sup>4</sup>

Variety of pretreatments ranging from topical anesthesia of larynx to administration of several classes of drugs like nitroglycerine,  $\beta$  receptor blocking agents and opioids have been identified. Each technique has its own advantages as well as disadvantages. Multimodal therapy is in practice to attenuate this response.<sup>5</sup> Dexmedetomidine a selective  $\alpha_2$  agonist provides multimodal features like sedation, hypnosis, analgesia and sympatholysis. It also decreases levels of catecholamines during surgery and maintains intra operative hemodynamics. Esmolol is a highly selective  $\beta_1$  blocking drug which is used mainly for peri

operative control of BP and hemodynamic stability. Since both, an age old established  $\beta_1$  blocker esmolol and highly  $\alpha_2$  specific agonist dexmedetomidine act upon sympathetic system through different means we chose to compare and find out which of these drugs is more helpful in lessening the stress response.

### Materials and Methods

After obtaining the institutional scientific and ethical committee approval and consent of patient and patients relatives, 102 patients belonging to age group of 18-65 years with ASA physical status I/II undergoing different operative procedures requiring general anesthesia, were taken in the study whereas patients with allergy or contraindications to the study drug, patients with anticipated difficult airway, pregnant patients or lactating patients, morbidly obese patients, patients suffering from cardiac illness, diabetes, patients with heart rate < 60 bpm and systolic blood pressure < 100 mmHg were excluded from our study.

All of the 102 patients were distributed into two groups with 51 patients based on simple randomized technique to receive the study drugs. Group D- Dexmedetomidine group (n=51): received injection Dexmedetomidine ( $1\mu\text{g} / \text{kg}$ ) diluted to 10 ml with normal saline intravenously over 10 min using a syringe pump. Group E - Esmolol group (n=51): received Inj Esmolol  $1\text{mg}/\text{kg}$  diluted to 10 ml with normal saline over 60 seconds. Once the patient arrived into the operation theatre, a dragger multi parameter monitor was attached and intravenous cannula preferably of 20 G was inserted and connected to ringer lactate fluid. 5 minutes after the patient settled in the theatre, baseline of all the hemodynamic and respiratory parameters were recorded. (heart rate and rhythm, blood pressure i.e systolic, diastolic, and mean arterial pressure,  $\text{O}_2$  saturation, and ECG). After that all the patients were given premedication with Glycopyrrolate  $0.005\text{mg}/\text{kg}$ , to decrease the oral secretions occurring either due to drugs or airway manipulations during intubation; midazolam  $0.03\text{mg}/\text{kg}$  and fentanyl  $2\mu\text{g}/\text{kg}$ . The study drugs were given as mentioned below 3minutes prior to intubation.

Group D received dexmedetomidine  $1\mu\text{g}/\text{kg}$  body weight diluted in 10 ml normal saline intravenously over 10 min, using syringe pump (Drug preparation:  $100\mu\text{g}$  of dexmedetomidine (1ml) was added to 9.0 ml of normal saline and made to 10 ml with each ml

containing  $10\mu\text{g}$  of dexmedetomidine). Group E received inj. Esmolol  $1\text{mg}/\text{kg}$  body weight diluted to 10ml over 60seconds. This study was not blinded as the rate of drug administration varies.

Preoxygenation was done for 3mins, patients were induced with sevoflurane (adjusted till loss of verbal response). Orotracheal intubation was facilitated with IV Vecuronium bromide  $0.1\text{mg}/\text{kg}$  three minutes prior to laryngoscopy and intubation. Intubation was performed using appropriate sized Macintosh blade lasting for not more than 15 seconds and after confirmation of bilateral equal air entry, the endotracheal tube was fixed. If time for laryngoscopy and intubation exceeded 15 seconds or intubation required more than 2 attempts such patients were excluded from the study. Anesthesia was maintained with oxygen and nitrous oxide, in the ratio of 30:60, sevoflurane (end tidal 1.5%) and incremental doses of vecuronium bromide. No surgical or any other stimulus was applied during 10 minutes of study period. At the end of the procedure patients were reversed with neostigmine  $0.05\text{mg}/\text{kg}$  and glycopyrrolate  $0.02\text{mg}/\text{kg}$ .

Heart rate, systolic blood pressure (SBP), diastolic blood pressure(DBP),mean arterial pressure(MAP) and rate pressure product(RPP) were measured at the following time periods base line before giving study drug, 2 minutes after study drug, 1 min after induction, 1 minute, 2 minutes, 3 minutes, 5 minutes after intubation respectively.

Side effects like fall in B.P, tachycardia, bradycardia or any type of dysrhythmias were also noted. Statistical analysis: The statistical software namely Microsoft excel, SPSS version 20, Open Epi version 2 were used for analysis of data and to generate graphs, tables etc Sample size was calculated with 80% of power analysis and 95% as confidence level and 10% as the absolute error. Demographic data of the patients were expressed in the form of mean  $\pm$  standard deviation. The statistical data were analysed by paired student's t-test for intra-group variations of values and unpaired t-test for inter-group variations. Values were considered important when  $p < 0.05$ .

### Results and Discussion

The groups were comparable with respect to age, weight, ASA physical status, gender as well as the type of surgeries underwent (table1)

**Table 1: Demographic profile**

	Group D	Group E
Age (Mean $\pm$ S.D)	31.902 $\pm$ 10.1296	33.039 $\pm$ 11.14
Male:Female	33.3:66.7	33.3:66.7
Weight(KG)	56.667 $\pm$ 8.799	56.667 $\pm$ 8.799
Surgeries		
Lap appendicetomy	38	40
Lap cholecystectomy	06	04

Thyroidectomy	07	06
Miscellaneous(Cystogastrostomy)		01

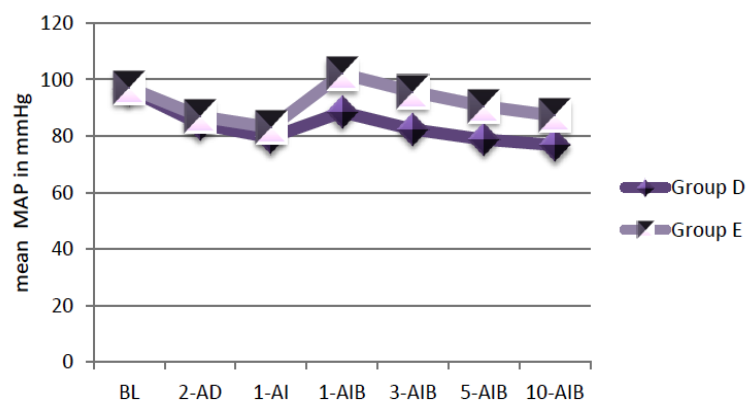
Baseline heart rate, mean arterial pressure were comparable in both the groups The mean HR decrease observed at 3, 5 and 10minutes after intubation in Group D was statistically highly significant compared to mean HR in group E ( $p < 0.000$ ). (table 2)

**Table 2: Comparison of mean heart rate (bpm) changes in response to laryngoscopy and intubation between group D and group E**

Time	Group D	Group E	p-value	t-value
Baseline	5.78 ± 11.85	89.64±10.54	0.085 (NS)	1.7354
2 min after drug	72.37±12.89	76.15±8.81	0.086 (NS)	1.7304
1 min after induction	71.01±11.19	75.03±8.87	0.47 (S)	20.103
1 min after intubation	84.03±10.83	97.76±10.40	0.000 (HS)	6.5239
3 min after intubation	78.07±10.53	91.09±9.26	0.000 (HS)	6.6270
5 min after intubation	74.52±11.04	85.98±8.91	0.000(HS)	5.7607
10 min after intubation	72.70±10.02	82.09±9.00	0.000 (HS)	4.9769

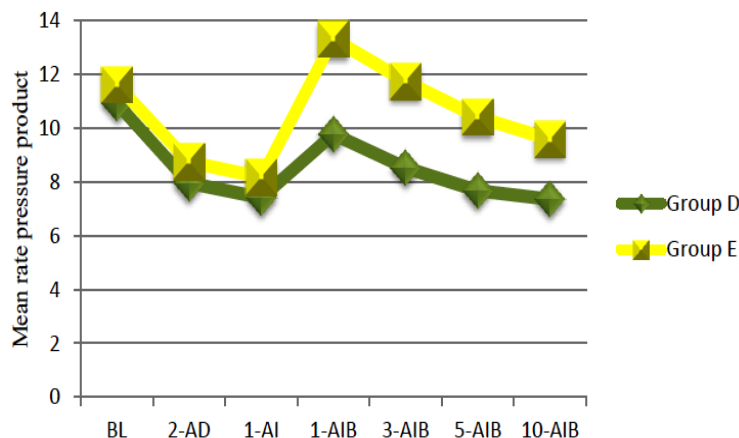
The mean fall in SBP in group D at 1, 3, 5 and 10 minutes after intubation was statistically highly significant ( $p = 0.000$ ) compared to the Esmolol group E The fall in mean DBP value at 1,3, 5 and 10 minutes of intubation were statistically highly significant ( $p = 0.000$ ) in group D compared to the latter group.

The mean basal MAP, 2min after drug administration and 1min after induction are comparable in both groups ( $p > 0.05$ ). The fall in mean MAP values in group D at 1, 3, 5 and 10 minutes of intubation were statistically highly significant ( $p < 0.0000001$ ) compared to group E.



**Fig. 1: Mean of MAP (mmHg) changes in response to laryngoscopy and intubation between group D and group E**

1 min after induction fall in mean RPP value in group D is statistically higher than in group E ( $P = 0.0243$ ). The fall in mean RPP values in at 1, 3, 5 and 10 minutes of intubation were statistically highly significant ( $p < 0.0000001$ ) compared to group E. [RPP calculated by formula  $(SBP \times HR) / 1000$ ]



**Fig. 2: Mean rate pressure product changes in response to laryngoscopy and intubation between group D and group E**

(Rate pressure product (RPP) is a term used in cardiology, as well as exercise physiology, to measure the workload or oxygen demand of the myocardium and reflects hemodynamic stress.)

**Side effects/Complications:** We noticed 10% incidence of hypotension and a fall in heart rate in 6% of study group in group D which did not require any intervention. However none of the patients in group E had these side effects.

### Discussion

During the induction of general anesthesia insertion of laryngoscope and insertion of tracheal tube play a critical role as they provoke transient but marked sympathetic response which could be detrimental in patients of cardiac illness.<sup>5-7</sup> This in turn results in increase in blood pressure and heart rate and hence the rate pressure product (RPP). A high RPP indicates a potential danger of myocardial ischaemia. As these adverse hemodynamic effects are controlled through sympathetic nervous system and therefore may be suppressed by supplementing drugs which blocks adrenergic receptors. Many adjuvants like  $\beta$ -blockers, opioids, calcium channel blockers,  $\alpha_2$  agonist drugs and esmolol or combinations have been tried in various studies, for blunting of hemodynamic responses, but if these adjuvants were used in higher than normal doses it had led to increased incidence of side effects.

Rathore A et al<sup>24</sup> study came to a conclusion that esmolol is useful in attenuating the rise in mean pulse rate to airway manipulation with all doses like (50,100, 150 mg/kg) but fall in BP was significant only with higher dose ( $p=0.000$ ).The RPP reduced with higher doses of the drug used mainly at 150mg) but was associated with significant adverse effects (hypotension and bradycardia)

Bensky and colleagues<sup>22</sup> suggested that small doses of Esmolol (0.2-0.4mg/kg) may reduce the rise in HR and BP resulting from airway stimulation. Singhal et al<sup>19</sup> found that when esmolol 1.5mg/kg was administered 3min prior intubation, increase in SBP and RPP was statistically not significant  $p > 0.05$ . In view of above study we employed administration of esmolol 3min prior intubation.

Based on the above studies low doses of esmolol like 0.2mg-0.4mg are also effective to reduce heart rate and blood pressure as concluded by Bensky et al and based on the study of Rathore et al all doses like 50mg, 100mg, 200mg were effective but more effective with higher doses but higher doses are also associated with adverse effects. This made us to proceed with a dose of esmolol 1mg/kg.

Sharma et al<sup>23</sup> reported that the increase in MAP was not statistically significant after intubation ( $P > 0.05$ ) with esmolol 100mg, the arterial pressures were comparable to basal values and they noticed a profound fall in MAP ( $P < 0.001$ ) with esmolol 200mg. The probable reason for not having achieved a better response even with 100mg Esmolol is that they conducted their study on treated hypertensive patients.

The purpose of our study was to know the usefulness of Dexmedetomidine at a dose of 1 $\mu$ g/kg and Esmolol at a dose of 1mg/kg in lessening the hemodynamic response to laryngoscopy and endotracheal intubation. In our study dexmedetomidine was diluted in normal saline and given over 10 minutes using syringe pump to prevent transient rise in B.P. and HR that occur due to peripheral  $\alpha_2$  adrenoceptors stimulation of smooth vessels in the vessels. The administration of dexmedetomidine as 10 ml in the present study is similar to the administration by Scheinin et al<sup>17</sup> and the timing of administration of dexmedetomidine was chosen from the pharmacokinetic profile (distribution  $t_{1/2}=6$ min).

We have induced the patients with sevoflurane rather than propofol as the fall in BP associated with propofol is more profound 10-40%.<sup>20,21</sup>

Jaakola and colleagues<sup>25</sup> noted that after insertion of endotracheal tube the maximum heart rate was 18% less ( $p=0.036$ ) in group D compared to placebo group. Within 10 min after intubation maximum systolic and diastolic pressures were also significantly ( $p=0.013$  and  $p=0.020$ ) smaller in dexmedetomidine group.

In our study, the fall in HR was statistically significant ( $p<0.05$ ) at 1min after induction of general anesthesia and statistically highly significant ( $p<0.0000001$ ) after intubation in group D. The fall in MAP and RPP was comparable in both the groups before intubation ( $P>0.05$ ), but we found statistically highly significant fall in MAP in group D ( $p<0.0000001$ ) than in group E. Hence dexmedetomidine decreases the cardiac energy requirements more effectively than esmolol at the above mentioned dosage.

Our study also noted similar finding that esmolol reduced the rise in HR and BP and the reduction was higher compared to study conducted by Bensky and colleagues<sup>22</sup> as we chose a higher dose. In our study we found a significant but a lesser rise in arterial pressures than the study conducted by Rathore A et al,<sup>24</sup> probably due to concomitant use of fentanyl which itself is a proven attenuator of stress response. But we do not consider it as a confounding factor as it was used in both the study groups.

We have found a greater fall in the HR, SBP, and DBP than Jaakola's study<sup>25</sup> due to the greater dose of dexmedetomidine used. Our results coincide with study conducted by Keniya et al<sup>26</sup> who found a significant fall in HR and BP with use of  $1\mu\text{g}/\text{kg}$  dexmedetomidine ( $p=0.000$ ). Yavascaoglu<sup>27</sup> found that the amount of reduction in HR in dexmedetomidine group ( $0.5\text{mg}/\text{kg}$ ) was higher than esmolol group ( $0.5\text{mg}/\text{kg}$ ) ( $p=0.046$ ). MAP at 1min after intubation in dexmedetomidine group was significantly less than that in esmolol group ( $p=0.012$  and  $p=0.005$  respectively). Our study shows highly significant difference probably due to higher doses of study drugs used.

We noticed 10% incidence of hypotension and a fall in heart rate in 6% of study group in group D which did not require any intervention. However none of the patients in group E had these side effects, we attribute this to the lower dose of esmolol used.

Unlike other studies we have used fentanyl in our study which probably led to better attenuation even with small dose of esmolol.

## Conclusion

Our study lead to the conclusion that Dexmedetomidine  $1\mu\text{g}/\text{kg}$  was more effective in attenuating the pressure response to laryngoscopy and intubation when compared to esmolol  $1\text{mg}/\text{kg}$ .

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