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A Randomized Control Study comparing effect of Intravenous Dexmedetomidine vs Intravenous Esmolol on attenuation of Pressor Response to Laryngoscopy and Endotracheal Intubation.

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Abstract
Background: During general anesthesia airway control is usually provided by laryngoscopy and endotracheal intubation. These are noxious stimuli leading to extreme haemodynamic stress and is associated with intense sympathoadrenal response marked by tachycardia, hypertension and arrhythmia which can be deleterious to pateients. The Aim of our study was to compare effects of IV dexmedetomidine with esmolol in attenuating the pressor response du ring laryngoscopy and intubation.
Methods-90 patients of ASA I and ASA II grade between 18-65 yr scheduled for elective non cardiac surgery under general anaesthesia.The patients were randomly divided into three groups(n=30).Group C received placebo,Group E received 1.0 mg/kg of esmolol and group D received 1µg per kg of dexmedetomidine intravenously over 15 min and just before induction.All patients were uniformly premedicated,induced with thiopentone and rocuronium as per standard protocol.Heart rate(HR),blood pressures(BP) were recorded at baseline,after study drug infusion,after induction,immediately and 1,3,5,10 min after intubation.
Results: Demographic parameters were comparable between the groups. The heart rate and blood pressure was significantly increased in patients receiving placebo and esmolol after laryngoscopy and intubation compared with baseline value and Group D. The rise in HR and BP at the time of laryngoscopy and intubation were minimal with statistical significance in Group D.
Conclusion: Both esmolol and dexmedetomidine attenuated the pressor response.Of the two drugs administered dexmedetomidine 1µg / kg provides a reliable, consistent and effective attenuation of pressor response as compared to esmolol 1.0 mg/kg.
Keywords: Dexmedetomidine, esmolol, , intubation, laryngoscopy, hemodynamic response

I. INTRODUCTION:

During general anesthesia, airway control is usually provided by laryngoscopy and endotracheal intubation ,resulting in mechanical and chemical stimuli. Mechanical stimulus causes reflex responses in cardiovascular and respiratory systems which reaches its maximum level within 1 min and ends in 5-10 min after endotracheal intubation, whereas chemical stimulus results in catecholamine release due to increase in sympathoadrenergic activity. Release of catecholamine leads to tachycardia, hypertension and arrhythmia. Tachycardia generates a more powerful load on the heart when compared with hypertension as it increases oxygen consumption of the myocardium, decreases diastolic filling and finally reduces coronary blood supply.[1,2]

The extent of pressor response to laryngoscopy and intubation is related to patient's age, depth of anaesthesia and presence of any comorbidities[3].Various drugs like Narcotic analgesics[4,5], local anesthetics[6,7], calcium channel blockers[8,9], beta-blockers[10,11], vasodilators[12,13], and alpha 2 adrenergic[14] agonist have been used to control that response.

Dexmedetomidine is highly selective and specific α-2 adrenoreceptor agonist that helps in haemodynamic stability and attenuation of sympathoadrenal responses during laryngoscopy and tracheal intubation. Esmolol is ultra-short-acting, beta-adrenergic receptor antagonist effective in providing haemodynamic stability during laryngoscopy and tracheal intubation without severe side effects.[15]

This topic for study was selected as various drugs have been used to attenuate pressor response to laryngoscopy & intubation, only with limited success, due to adverse effects of the drugs at varying doses. So there is continous search for a drug that attenuates pressor response, with fewer adverse effects & could be used in maximum patients of various ASA grades posted for surgery under general anaesthesia.Variuos previous

studies were biased towards any one agent as the two drugs had to be administered in different manner, so here we compared the two drugs with different design to get advantage by obtaining most suitable dosage form.

In this study, we compared safety and efficacy of single bolus intravenous dose of dexmedetomidine with single bolus intravenous dose of esmolol in attenuating hemodynamic response to laryngoscopy and tracheal intubation.

II. MATERIALS AND METHODS

This randomized, prospective, double-blind, controlled study was carried out in the department of anaesthesiology, MGIMS, sewagram Maharashtra after approval of Institutional Ethical Committee. 90 normotensive patients of ASA I-II grade between 18-65 yrs of either sex scheduled for elective surgery (non cardiac) under general anaesthesia requiring endotracheal intubation were included, Excluded patients were those who refused giving consent, patients with anticipated difficult intubation (Mallampati grades III ,IV), or who were hypertensives or had respiratory, cardiovascular ,neurological, psychological, hepatic, renal and endocrinal disease or on any medication like sedatives or opioids, alcohol abuse history or drug allergy, lactating or pregnant patients. Study was carried out in period ranging between years 2015-2016 over 18 mnths.

Informed written consent for study in patient's language was taken and patient were randomly allocated into 3 groups of 30 each by computer generated table. Group D(n=30) - Dexmedetomidine group received IV dexmedetomidine infusion before induction of anaesthesia.Group E(n=30) - Esmolol group received IV esmolol at the time of induction of anaesthesia.Group C(n=30) - Control group received no drug but only normal saline.

On the day prior to surgery a thorough pre-operative assessment of the patient was performed including general physical & systemic examination.All patients were explained about anaestheia technique & written informed consent was taken. Patients were kept NBM for 6 hrs prior to surgery Patients premedicated with oral oral ranitidine 150 mg and Alprazolam (0.25 mg) on night before surgery. In the operating room, standard monitors (ECG, Noninvasive blood pressure and pulse oximeter) were attached to the patient , and baseline vitals namely heart rate (HR),pulse oximetry (SPO2), blood pressure(BP), Mean Arterial Pressure (MAP), respiratory rate (RR) and Electrocardiogeram (ECG) were recorded.After securing an 18G IV line,patients were preloaded with 10 ml /kg ringer's lactate. Drugs involved in study were premixed to appropriate volume and presented as coded syringes by an anesthesiologist not involved in study. All patients were blinded to study group and an anaesthesiologist who was unaware of study drug recorded observations. Thus study was double blinded.

Anaesthesia technique

Anaesthesia machine and breathing circuits checked, resuscitation equipments were kept ready. Vital parameters were continuously monitored .All study patients were premedicated with IV gylcopyrolate 0.2mg and midazolam 1mg. *Group D* patients received IV Dexmedetomidine at 1µg/kg in 100 ml normal saline over 15 min. At the end of infusion, pre-oxygenation with 100% oxygen was started and loading dose of a placebo(normal saline) IV injection of volume in milliliters equal to 1/10th of the body weight was given at the time of induction of anaesthesia.

Group E patients received IV normal saline 100 ml over 15minutes and at the end of infusion, pre-oxygenation with 100% oxygen was started and esmolol in a dose of 1mg/kg (10mg/cc) was given at the time of induction of anaesthesia.*Group C* patients received IV normal saline 100 ml over 15 minutes via infusion pump. At the end of infusion, pre-oxygenation with 100% oxygen was started and loading dose of a placebo(normal saline) IV injection of volume in milliliters equal to 1/10th of the body weight was given at the time of induction of anaesthesia.

Induction of ananesthesia was carried out with IV fentanyl 2 µgm/kg and IV thiopentone sodium in a dose of 5mg/kg followed by IV rocuronium 1mg/kg to provide neuromuscular blockade. The patients were ventilated through bag and mask with 100% oxygen with Bains circuit for next 1.5 minutes. Thereafter, laryngoscopy was performed by senior anaesthesiologist with Macintosh laryngoscope and intubation done with a cuffed endotracheal tube of appropriate size within 30 seconds. Patients in whom intubation was not achieved within this period were excluded from the study. Strict and vigilant monitoring of haemodynamic and respiratory parameters at regular intervals of 1 minute, 3 minute, 5 minute and 10 minute after intubation was done. During the entire study period of 10 minutes , no form of surgical stimulus was applied.

Vital parameters recorded at following points of time:

1. Baseline reading when the patient shifted to the OT (To)
2. After infusion over 15 minutes (Ti)
3. After induction of anaesthesia(Ta)
4. Immediately after intubation(Te)
5. At 1 minute after intubation(T1)
6. At 3 minute after intubation(T3)
7. At 5 minute after intubation(T5)

8. At 10 minute after intubation(T10)

Statistical analysis was done by using descriptive and inferential statistics using Chisquare test, one way ANOVA and Multiple Comparison: Tukey Test and software used in the analysis were EPI-INFO 6.0 version, STATA, SPSS 17.0 version and GraphPad Prism 6.0 version. EXCEL spreadsheet was used for electronic data entry. Descriptive data presented as mean +/- SD. The comparisons considered as not significant ($p > 0.05$),significant ($p < 0.05$) or highly significant ($p < 0.001$) . Using the results of previously conducted study and considering an α error of 0.001 and β error of 1.282, with power of 90 % and p1 as 98 and p2 as 90, in the below stated formula the sample size of 30 in each group was derived.

$n = 2(Z\alpha+Z\beta)^2 (S1^2 + S2^2)$
$(x1- x2)^2$
Zα=3.29 , Zβ=1.282 , power=90% , q=6
S1= standard deviation of Esmolol group
S2= standard deviation of Dexmedetomidine group

III. RESULTS

The demographic profile of the patients in terms of age, body weight, male:female ratio, ASA status, Mallampati Class were comparable and no significant differences found among the three groups (P > 0.05).**(table 1)**

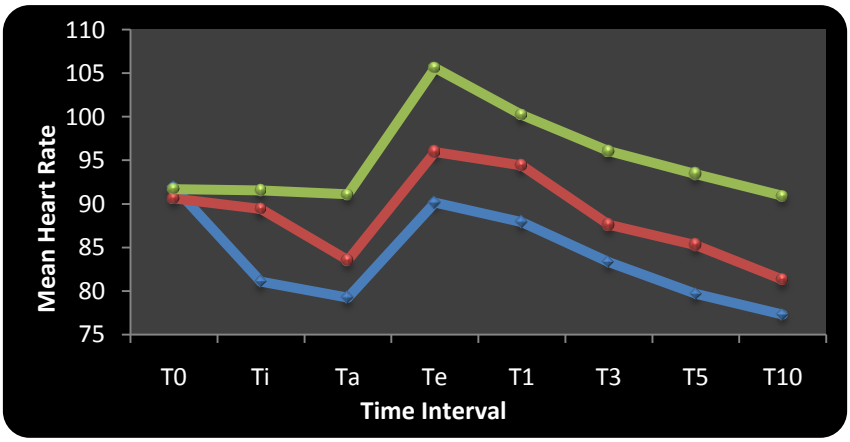
Table 1. Comparison of demographic data between 3 groups

Parameters	**Group D**	**Group E**	**Group C**	**p- value**
Age	37.3±12.39	34.36±10.34	36.96±12.35	0.689
Gender(m/f)	15/15	13/17	14/16	0.175
BMI(Body Mass Index)	23.98±2.52	23.89±2.89	24.67±1.42	0.89
ASA grade (I/II)	25/5	25/5	25/5	1.00
MPC grade(I/II)	15/15	17/13	18/12	0.73

The mean HR values Immediately after intubation ,In Group D there was 1.8 bpm decrease in mean HR compared to basal, in Group E there was 5.33bpm increase in mean HR and in Group C there was 13.93 bpm increase in mean HR compared to basal values. Immediately after intubation mean HR changes between group D and group C was highly significant (p=0.0001), and between group E and group C was also highly significant (p=0.0001) whereas mean HR between group D and group E was significant(p=0.041).**(graph 1)**

Mean HR rate values were lower in group D as compared to group C immediately after intubation ,similarly decreasing trend was observed in percentage change of mean heart rate at 1,3,5 and 10 minutes interval & was statistically significant(p=0.0001). When group D was compared with group E, mean HR was lower in group D immediately after intubation, at 1,3,5 and 10 minutes with statistically significant values at Te,T1,T5(p=0.041,p=0.010,p=0.015).**(graph 1)**

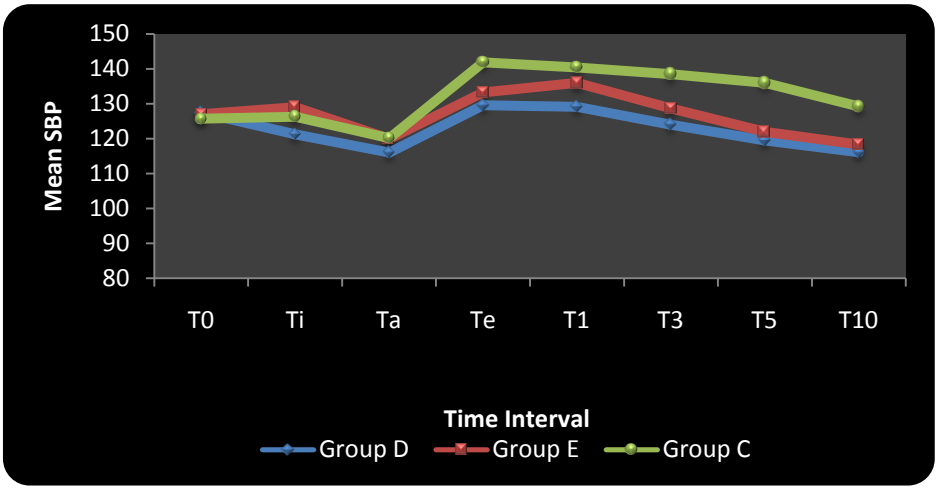
Graph 1: Comparison of heart rate in three groups



Mean SBP values were lower in group D as compared to group C immediately after intubation ,similarly decreasing trend was observed in percentage change of mean SBP at 1,3,5 and 10 minutes interval ,was statistically significant(p=0.0001). When group D was compared with group E, mean SBP was lower in

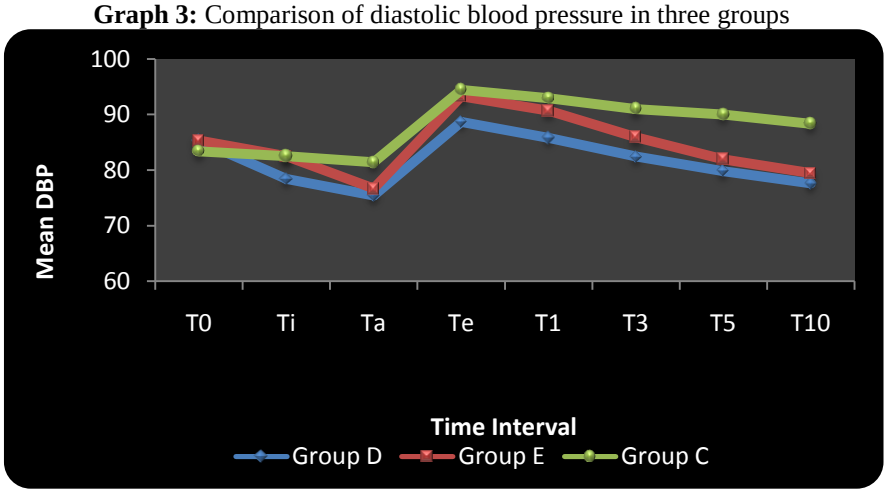
group D immediately after intubation, at 1,3,5 and 10 minutes with statistically significant values at Te,T1(p=0.038,p=0.005). Mean SBP rise in both study drug groups, group D & group E as a result of pressor response was less than group C.**(graph 2)**

Graph 2: Comparison of systolic blood pressure in three groups



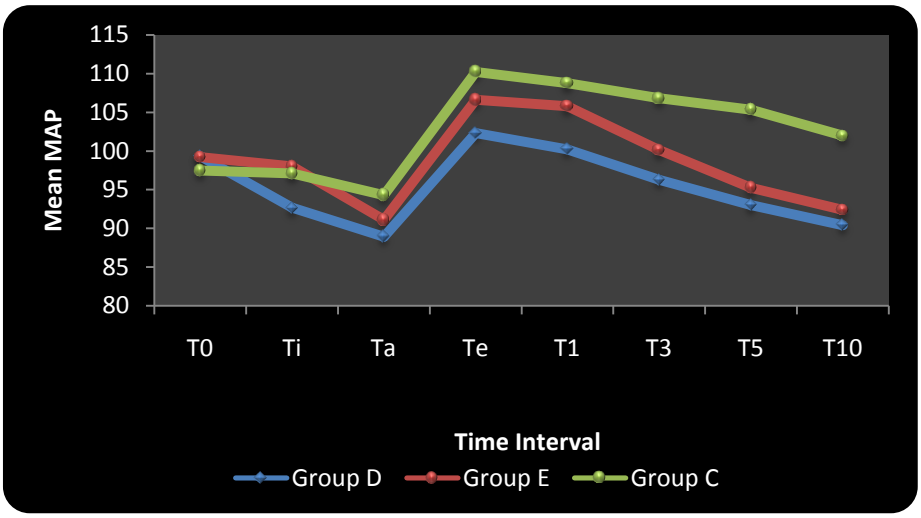
Mean DBP values were lower in group D as compared to group C immediately after intubation ,similarly decreasing trend observed in percentage change of mean DBP at 1,3,5 and 10 minutes interval ,was statistically significant($p<0.01$). When group D was compared with group E ,mean DBP was lower in group D immediately after intubation, at 1,3,5 and 10 minutes with statistically significant values at Te,T1($p<0.05$). Mean DBP rise in both study drug groups, group D and group E as a result of pressor response was less than control group C.**(graph 3)**

Graph 3: Comparison of diastolic blood pressure in three groups



Mean MAP values were lower in group D as compared to group C immediately after intubation ,similarly decreasing trend observed in percentage change of mean MAP at 1,3,5 and 10 minutes interval ,was statistically significant($p<0.01$). When group D was compared with group E mean MAP was lower in group D immediately after intubation, at 1,3,5 and 10 minutes with statistically significant values at Te,T1 and T5($p<0.05$). Mean MAP rise in both study drug groups, group D and group E as a result of pressor response was less than group C. But in group D attenuation was better and sustained throughout the study period compared to other 2 groups**.** In our study no significant differences in SpO2 ,Respiratory Rate and ECG were observed before and after injecting the drug, intraoperative and postoperative period between group D,E and C.($p>0.05$)**(graph 4)**

Graph 4: Comparison of Mean Arterial Pressure in three groups



IV. DISCUSSION

Most of the general anaesthesia procedures in modern anaesthetic practice are carried out with endotracheal intubation. Laryngoscopy and endotracheal intubation are considered to be the most critical events during administration of general anaesthesia, because they provoke transient but marked sympathoadrenal responses manifesting as tachycardia and hypertension[1]. These responses are usually transitory, variable and may not be significant in normal individuals, but in patients with cardiovascular disease like hypertension, Ischemic heart disease, Cerebrovascular disease and in patients with intracranial aneurysms even these transient changes in haemodynamics may result in potentially harmful effects like left ventricular failure, myocardial ischemia, pulmonary edema, ventricular dysrhythmias and cerebral haemorrhage[3].These are by far the most important indications for attenuation of haemodynamic response to laryngoscopy and endotracheal intubation[16]

Many methods like use of inhalational anaesthetic agents, lidocaine[6,7], opioids[4,5], ß-blockers[10,11], calcium channel blockers[8,9], direct acting vasodilators[12,13] have been tried by various authors for blunting haemodynamic responses to laryngoscopy and intubation. But most of such maneuvers had their own limitations. For example, with opioids respiratory depression and chest wall rigidity were potential problems, use of halothane was associated with dysrrhythmias, calcium channel blockers produced reflex tachycardia, direct acting vasodilators needed invasive haemodynamic monitoring and lidocaine showed in-consistent results in blunting the haemodynamic responses to laryngoscopy and intubation.Hence drugs which can blunt both the heart rate and blood pressure response to laryngoscopy and intubation, without having any adverse effects like respiratory depression and post operative nausea and vomiting(PONV) was required for the purpose.

Dexmedetomidine is highly specific and selective α-2 adrenoceptor agonist, results in attenuation of sympathoadrenal responses and haemodynamic stability during laryngoscopy and endotracheal intubation. The decrease in heart rate and BP following infusion of dexmedetomidine is result of stimulation of α2-adrenoceptors located within the central nervous system and blood vessels and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow and augmentation of vagal activity.[15]

Esmolol is an ultra-short-acting, cardioselective, beta-adrenergic receptor antagonist with known efficacy to provide haemodynamic stability during laryngoscopy and endotracheal intubation without severe side-effects. It attenuates tachycardia and hypertensive response by decreasing force of contraction and HR by blocking beta-adrenergic receptors of sympathetic nervous system which are found in heart, blood vessels and other organs. It also prevents action of two naturally occurring neurotransmitters, epinephrine and nor-epinephrine, resulting in attenuation of haemodynamic responses[15]

The present study was undertaken to evaluate the effects of single premedication dose of IV dexmedetomidine vs IV Esmolol in attenuating the pressor response to laryngoscopy and endotracheal intubation.

Dosages of drugs selected

Various authors have employed IV dexmedetomidine for blunting haemodynamic responses to laryngoscopy and intubation in different doses starting from 0.3 µg/kg to 1.0 µg/kg. Since most of the authors found dexmedetomidine effective at dose of 1µg/kg body weight in attenuating

pressor response to intubation, 1µg/kg body weight dose was chosen in this study. The dose selected in our study is similar as in the studies conducted by Yildiz et al[17], Kunisawa et al[18], Ferdi et al[19], Keniya et al.[20],

Sukhminder Jit et al.[21] Similarly various doses of IV esmolol have been employed for attenuation of haemodynamic responses to laryngoscopy and intubation

ranging from 0.2 mg to 2.0 mg/kg. While doses as high as 2 mg/kg were sufficient but were more likely to cause adverse side effects such as bradycardia and hypotension, doses as low as 0.2 mg/kg and 0.4 mg/kg were not sufficient for attenuating either tachycardia or hypertension, it has been found that 1 mg/kg is successful at alleviating some haemodynamic responses but is less efficient at attenuating others, especially blood pressure, similar effect was seen even at higher doses.[22] There is dose dependent risk of hypotension and bradycardia before

laryngoscopy when esmolol is combined with anaesthesia induction agents. In our study we used esmolol in dose of 1.0 mg/kg as there were complications such as bradycardia and hypotension with doses higher than 1.0 mg/kg and ineffective blunting of responses with doses less than 1.0

mg/kg .However the esmolol regimen used in the our study did not result in any deleterious haemodynamic effects. Similar doses were used by Bhagat et al.[23],Lakshmanappa et al[22] , Sree -krishna et al[24], Lakshmi et al[25].However no consensus has been reached regarding the optimum

dose and timing of its delivery.[26]

In our study dexmedetomidine infusion 1.0 µg/kg prior to induction of anesthesia suppressed hemodynamic response to laryngoscopy and endotracheal intubation. This suppression was found to be greater with dexmedetomidine than that resulted from esmolol 1.0 mg/kg. None of the patients developed complications like hypotension, bradycardia and desaturation due to our study drugs.

Yallapragada et al[27] found that dexmedetomidine is superior to esmolol in attenuating the haemodynamic response to laryngoscopy and tracheal intubation. they had higher readings of HR,SBP,DBP and MAP immediately after intubation ,might be due to low doses of Dexmedetomidine and Esmolol as compared to our study. Reddy et al[28] found that esmolol was not as effective on attenuating hypertensive response as it was on chronotropic response to tracheal intubation. In their study esmolol attenuated tachycardia better than dexmedetomidine ,it might be due to the higher doses of esmolol used in study, again higher doses were associated with complications such as bradycardia and hypotension which was not seen in our study.

However dexmedetomidine attenuated the rise in SBP,DBP,MAP better than esmolol which concurrs with our study. Gogus et al[29] in their study found Dexmedetomidine more effective than esmolol and fentanyl in preventing increase in heart rate, however esmolol was more effective in prevention of increases in systolic, diastolic and mean arterial pressures following endotracheal intubation, they used higher doses of Esmolol in their study. Mudgalkar et al[30]found that Dexmedetomidine and Esmolol were appropriate for attenuation of hemodynamic control ,however Dexmedetomidine provided more sustained hemodynamic stability suitable for long term control.

In our study, In dexmedetomidine group HR, SBP, DBP and MAP showed significant decrease throughout the study period when compared to control group.In Esmolol group there was significant decrease in HR when compared to control group but it was not much effective in preventing increase in SBP,DBP and MAP immediately after intubation and at 1,3 minutes, but later on at 5 and 10 minutes blood pressure values were significantly less as compared to control group.On comparing Dexmedetomidine group to Esmolol group, In Dexmedetomidine group there was significant decrease in HR SBP,DBP and MAP values immediately after intubation, at 1 min and 3 min, later at 5 and 10 minutes the groups were statistically comparable. Side effects like bradycardia, hypotension, nausea, vomiting, dryness of mouth, sedation were not observed in any of the patients and recovery was satisfactory.

Hence Esmolol 1 mg/kg attenuated chrontropic response significantly when compared to control group but was not much effective in attenuating hypertensive response whereas dexmedetomidine in the dose of 1µg/kg as IV infusion, given over 15 minutes, before induction significantly attenuated pressor responses to laryngoscopy and intubation. However the study has to be done on a larger population and in high risk patients for further evaluation.

V. CONCLUSION

From our study it can be concluded that Dexmedetomidine in dose of 1µg/kg IV when compared to Esmolol in dose of 1mg/kg IV before induction in patients scheduled for elective surgery under general anaesthesia,

- Attenuates pressor response during laryngoscopy and endotracheal intubation
- Decreases changes in heart rate, SBP, DBP and mean arterial pressure during laryngoscopy and intubation
- Provides haemodynamic stability without any side effects.

Therefore within the constraints of the study we demonstrated that, Of the two drugs administered, Esmolol attenuated the chronotropic response compared to control group but not hypertensive response whereas Dexmedetomidine 1.0 µg/kg provided a consistent, reliable and effective attenuation of pressure responses throughout the study period compared to Esmolol and control group. Hence it can be concluded that Dexmedetomidine is superior to Esmolol for attenuation of pressor response to laryngoscopy and intubation

without any side effects in patients without co-morbidities. Dexmedetomidine at dose 1μg/kg IV administered over 15 min, before induction is recommended over Esmolol 1mg/kg to attenuate hazardous haemodynamic response to laryngoscopy and intubation.

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