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Hemodynamic Changes with IV esmolol for attenuation of sympathomimetic response to laryngoscopy and endotracheal intubation in surgical patients – a comparative study

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ABSTRACT

Background : In 1986 esmolol, an ultra-short acting β1-cardioselective adrenergic receptor blocker was introduced which gained quick popularity for its short duration of action and nil risk of developing perioperative bradycardia or hypotension and found to be quite suitable to control the detrimental effects of laryngeal and tracheal stimulation. **AIM:** To compare the efficacy and safety of esmolol with normal saline in attenuating hemodynamic responses to laryngoscopy and intubation **in** patients of elective surgical procedures under general anesthesia. **Materials and method:** 60 patients of age 20 to 60 yrs,ASA physical status I and II posted for surgical procedures under general anaesthesia, randomized into two groups of 30 each to receive esmolol (Group E) 1.5mg/kg diluted to a total volume of 20 ml with 0.9% saline and control (Group C) 20 ml 0.9% saline ,both infused IV over a period of 10 min before 3 mins of induction. Changes in heart rate , systolic and diastolic blood pressure,rate pressure product (RPP), any side effects associated with the drugs during the study period i.e.,20 mins of intubation,were observed and statistically analysed. **Result :** between groups E & C there was statistically significant difference ($P< 0.0001$) in mean heart rate during intubation ,mean SBP (P=0.0001), mean DBP (P=0.0001) and mean RPP (P=0.0001) was observed.**Conclusion:** infusion of esmolol was found to attenuate the haemodynamic response to laryngoscopy and tracheal intubation significantly.

Keywords: Esmolol, general anaesthesia, tracheal intubation.

INTRODUCTION

Direct laryngoscopy,a successful way for tracheal intubation was first reported by Chevalier Jackson in 1913 .[1] In1943, Sir Robert Macintosh introduced curved laryngoscope blade which had made significant advancement in the technique of tracheal intubation .Hemodynamic changes as hypertension, tachycardia and /or arrhythmias [2,3] are almost always associated following induction of anaesthesia [4] which peak approximately 30-45 seconds after laryngoscopy due to reflex sympathetic discharge caused by the epipharyngeal and laryngopharyngeal stimulation and this was first reported by REID and BRACE in 1940 [5] and King Harris in 1951.[6] Larynx, pharynx, epipharynx and trachea are extensively innervated by the autonomic nervous system.Sensory afferents from epipharynx and laryngopharynx are mainly carried by glossopharyngeal nerve to vasomotor centre.Stimulation of proprioceptors at the base of the tongue during laryngoscopy induces impulse dependent increase in heart rate, systemic blood pressure ,intracranial pressure and plasma catecholamine concentrations[7] also dysrhythmias , cardiac asystole and even sudden death.[8] To attenuate the haemodynamic response to laryngoscopy & endotracheal intubation, various

non- pharmacological methods like medical condition of the patient, smooth and gentle intubation with shorter duration of laryngoscopy, anesthetic technique as insertion of Laryngeal mask airway in place of endotracheal intubation[9] route of administration of drugs or pharmacological methods such as Glossopharyngeal & superior laryngeal nerve blocks, choice of drugs[10] have been tried by different clinicians. Drugs commonly chosen are

Topical application: Transdermal Nitroglycerin patch

2. A) ACE inhibitors as captopril, enalapril prior to intubation, Ca^{++} channel blocker as sublingual nifedipine

b) Fentanyl, morphine,[11] droperidol etc which block central mechanism of integration of sensory input

c) Intravenous lignocaine [12]

d) Clonidine, hydralazine, nitroglycerin [13]

e)Sodium nitroprusside,beta blockers [14] etc which block efferent pathway and effector site.Esmolol, an ultra-short acting β1-cardioselective adrenergic receptor blocker with a distribution half-life of 1 to 2.03 min and an elimination half-life of 9.19 [15] min appears to be quite suitable for use during tracheal intubation to attenuate a short lived stress. The doses of the drug may be prescribed as repeat boluses of 25 mg or as intravenous infusion of 25 to 300 µg/kg/min. It is inactivated by esterases in blood; plasma t½ is < 10 min; action disappears 15–20 min after terminating IV infusion. Esmolol undergoes very rapid metabolism by plasma esterases present in the red blood cells. Metabolism is not influenced by renal or hepatic dysfunction. Acid metabolite of esmolol is an extremely weak beta blocker. Excretion of the drug is less than 2% unchanged in urine.

We have chosen esmolol infusion for one group and compared it with a control group for attenuation of stress response during laryngoscopy and tracheal intubation.

Aim

To evaluate the drug esmolol in laryngoscopy and intubation procedures for attenuation of sympathomimetic responses in patients of elective surgeries under general anaesthesia.

Objectives

Primary

To study the efficacy of injection esmolol in intravenous infusion during laryngoscopy and endotracheal intubation in attenuating the

a) changes in heart rate (HR),

b) changes in systolic (SBP), diastolic (DBP) pressure

Changes in myocardial oxygen demand by using the rate pressure product (RPP).

Secondary

To evaluate the side effect if any associated with the use of the drugs during the study period.

MATERIALS and METHOD: The study had been conducted over a period of two years during 2016 to 2018 in the Department of Anaesthesia, Acharya Vinoba Bhave rural Hospital, affiliated to Jawaharlal Nehru Medical College, Sawangi (Meghe), Wardha . Approval from the institutional Ethics Committee and written informed consent from the patients in their vernacular language were obtained.

Study design

It is a prospective, randomized, interventional study.

Study Groups

60 patients, aged 20-60 years, weight between 40-70 kg, either gender, of American Society of Anesthesiologists' physical status I or II scheduled for elective surgical procedures were included in this study.

Inclusión Criteria:

- Endotracheal intubation using Macintosh laryngoscope for the patients scheduled for elective surgeries
- Mallampati airway assessment of Grade I and II

Exclusión Criteria:

- Unwilling patient.
- Emergency Surgeries
- Age less than 20 yrs or above 60 yrs.
- Patient with ASA Grade III or higher
- Patient with a history of known allergies to study drugs

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- Anticipated difficult intubation according to LEMON criteria/more than one attempt of intubation /nasal intubation /retrograde intubation
- Pregnant patient and breast feeding mothers
- Patient on Beta blockers /Calcium channel blockers /sympatholytic drugs or Pregabalin

Systemic illness such as hypertension, cardiovascular diseases, severe respiratory diseases, diabetes, hepatic failure, renal failure, hyperthyroidism or endocrine disorders. Routine pre-anesthetic evaluation of all patients done a day before the surgery, tablet alprazolam 0.5 mg was given the previous night of surgery to allay anxiety and kept nil by mouth for 6 hours before the surgical procedure. Patients were shifted to the operation theatre 15 mins prior to induction. Intravenous access secured with 18G IV cannula, noninvasive BP, pulse oximeter, ECG monitor and end-tidal carbon dioxide ($EtCO_2$) had been attached. Heart rate (HR), systolic (SBP), diastolic (DBP) blood pressure recorded had been considered as baseline value. Injection ondansetron 0.08 mg/kg as anti-emetic, glycopyrrolate 0.004mg/kg as an antisialogogue, had been given intravenously and infusion of normal saline started at the rate of 2ml/kg/hr.

Groups allocation was done randomly with the help of a computer generated table of random numbers into two groups of 30 patients each. An independent anesthesiologist not involved in the study, prepared the drugs to be infused with infusion pump in identical syringes.

*Group E (esmolol) study group (N= 30):1.5mg/kg diluted to a total volume of 20 ml with 0.9% saline IV over a period of 10 min.

*Group C (control) (N= 30): 20 ml 0.9% saline IV over a period of 10 min Immediately after , the patients were preoxygenated with 100% O_2 for 3 min, induced with injection propofol 2 mg/kg ,injection atracurium besylate 0.5 mg/kg,IPPVcontinued with 100% O_2 , laryngoscopy had been done after adequate relaxation (3-4 minutes) using standard Macintosh blade.Laryngoscopy used to be limited to ≤ 30 seconds by a consultant and intubation done with appropriate sized, disposable, high volume low pressure, portex cuffed endotracheal tube in all the cases in one intubation attempt which is defined as an act of introducing laryngoscope blade between the incisors into the oropharynx to achieve the endotracheal view.

If any patient in any group required external laryngeal manipulation to improve glottis visualization which caused more response to laryngoscopy, or if significant hypotension or bradycardia would occur during the study period, was dropped from the study. All the patients were ventilated with closed circuit and General anaesthesia was maintained with oxygen 40% and air 60 %, sevoflurane 1-1.5%, inj fentanyl 2 µg/kg and intermittent boluses of injection atracurium.

HR, SBP, DBP and RPP (rate pressure product) were recorded before administration of study drugs (BL),immediately after study drug given (IAS), during intubation (DI)and at 1(T1), 3 (T3), 5 (T5), 7(T7), 10(T10),15(T15)and 20 (T20) min after intubation .No surgical intervention was allowed during the study period.The end point of our study period was at T20 i.e.,20 min after intubation.

Statistical analysis was entered using Statistical Package for Social Service(SPSS 22.0 version) and Graph Pad Prism 5.0 version .Analysis for parametric data mean (M) and standard deviation (± SD) student's unpaird t test and for non-parametric data chi square test was done.$p<0.05$ is considered as level of significance.

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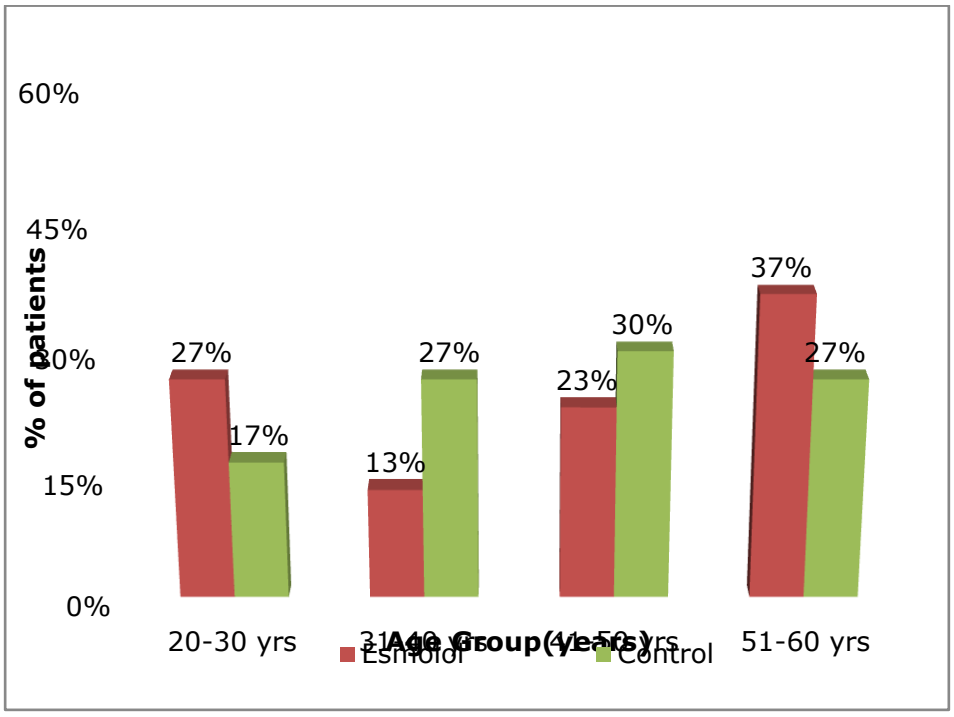
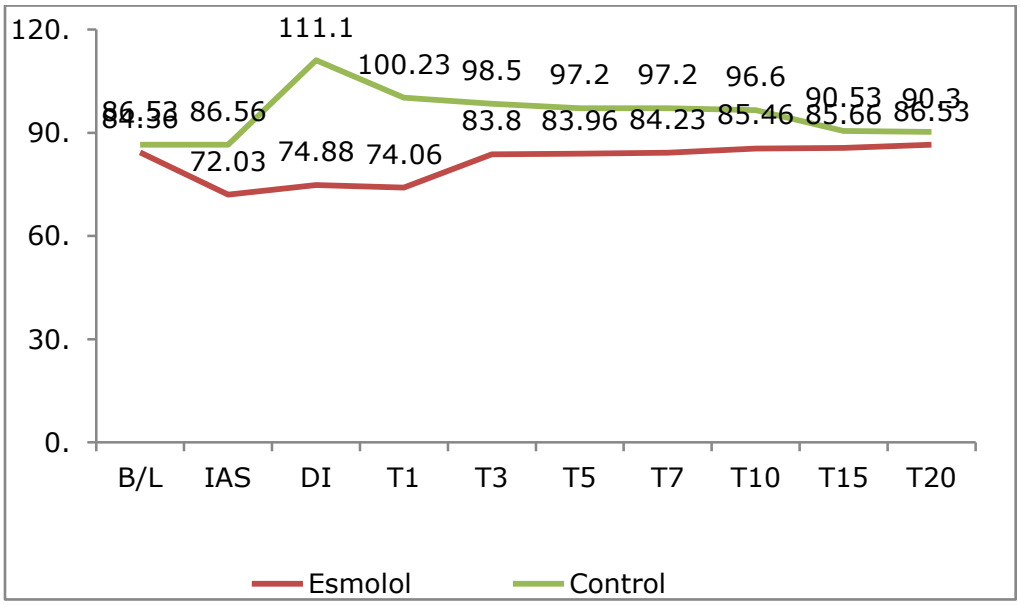
RESULT

Graph 1: Age group distribution of patients in two groups in percentage



Graph 2 : Comparison of changes in mean heart rate values at different time intervals



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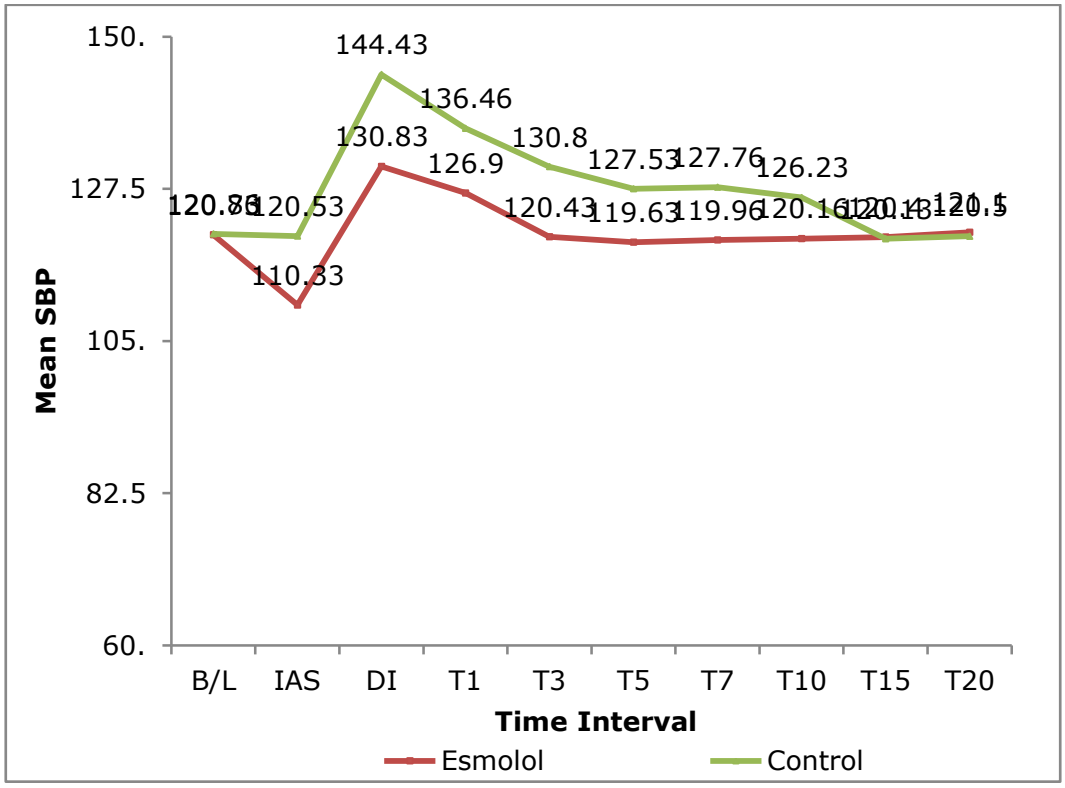
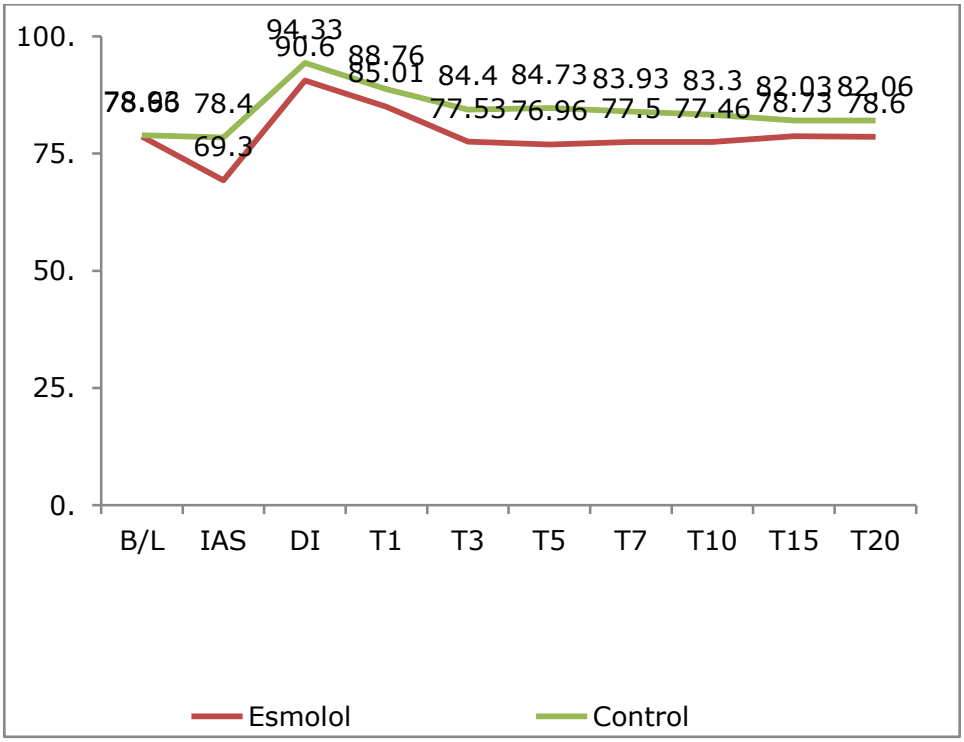
Graph 3: Comparison of changes in SBP values at different time intervals



Graph 4: Comparison of changes in DBP values at different time intervals



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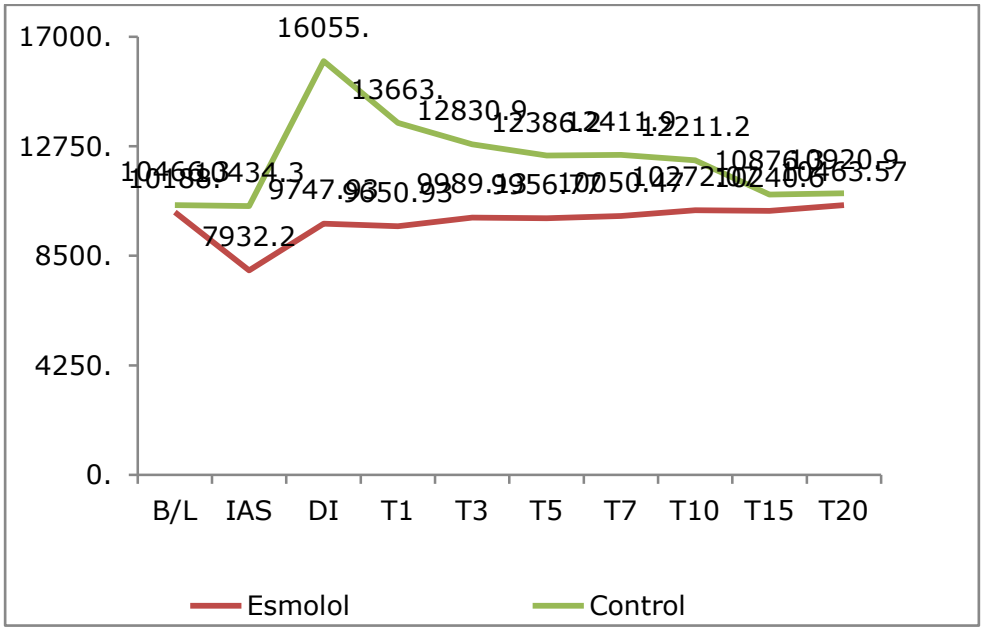
Graph 5: Comparison of changes in RPP values at different time intervals



DISCUSSION: Reid and Bruce et al [5] in 1940 were the first to recognise the hemodynamic responses such as hypertension, tachycardia ,atrial and ventricular extra-systoles, delayed conduction time following laryngoscopy and endotracheal intubation.KING and his associates [6] in 1960 reported that the reflex mechanism was probabaly due to increased sympathetic adrenal or decreased parasympathetic activity.Tachycardia ,a pressor response consistently accompanied tracheal intubation done under light general anaesthesia was observed by Devault M, Greifenstein FE et al in 1960 and they tried pharmacological drugs to tackle the ill effects. [16] But the method was short lived because the authors observed an exaggerated fall in blood pressure during peri operative period. Forbes AM et al observed an average increase in MAP of 25 mm of Hg **immediately** after laryngoscopy and endotracheal intubation. [11]

Bachofen M in their study for preventing sympathetic response cited that there happens a linear increase in heart rate and blood pressure mainly systolic, during first 45 seconds of laryngoscopy.[17] In our study,we have limited laryngoscopy and intubation timing to ≤ 30 second.

In1986, when esmolol, a selective beta-blocker was introduced, many investigators used it because of its short duration of action having no risk of developing perioperative bradycardia or hypotension.[18] Sharma et al [19] in their study concluded that 1-1.5mg/kg is most effective in attenuating haemodynamic responses during laryngoscopy and intubation without major adverse effects.So we used smaller dose of inj.esmolol (1.5mg/kg) in our study. None of our patients developed any side effects like severe hypotension (fall in BP > 25% as compared to baseline).

The drug administered in our study, was in infusion for 10 min followed by laryngoscopy and intubation 3 minute later .[20] Reddy S V et al [21] in 2014 in their study of 30 patients each in control group (C) who received 10 ml of physiologic saline, group (E) esmolol 2.0 mg/kg and Group D received dexmedetomidine 1.0 µg/kg ,all the drugs as slow IV infusion over a period of 10 min.The mean increase was minimal 5.83% in Group D (4 beats, P = 0.0848), when compared with Group E 14% (9.81beats; P = 0.0152) and Group C 30% (24.9 beats; $P < 0.0001$), which was highly significant ($P <$ 0.0001). The mean SAP levels in Group D were significantly lower than Groups C and E immediately after intubation ($P< 0.001$, $P> 0.001$ respectively).

In our study during larygoscopy and intubation there was a fall in mean heart rate in esmolol group by 11.24% and in control group a rise of 28.39% with a significant statistical difference ($P< 0.0001$). The

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mean SBP in esmolol group from DI [130.83±14.26 (8.36%)] to T1 [128.9±22.08 (6.76%] had a rise and afterwards from T3[120.43±12.07(0.24%)]to T20[121.1±10.86 (0.30%)] it started receding to reach the baseline value. In control group there was no attenuation of mean SBP but a rise by 19.50% from its baseline with a mean of (144.43±12.28)(P=0.0001) indicating that patient in group C were having a significant rise in mean SBP during laryngoscopy and intubation. M. Saif Ghaus et al [22] in 2002 studied an infusion of 300 g \ kg-1 \ min-1 esmolol for 4 minutes before induction and 200g kg-1 \ min-1 for maintenance for additional 6 minutes during intubation in study group and 5% dextrose infusion in control group of 50 patients each. They found the mean DBP in the study group was significantly different statistically in comparison to the control group (p value <0.01) at all the time intervals. We also had similar finding where at T1in esmolol group and in control group, a rise by 8.07% and 12.45% respectively above its baseline value.(P=0.0001,S). From T3 [77.53±8.52 (1.44%)] to T20 [78.6±8.10 (0.46%)] the DBP in esmolol group started reaching the baseline value. In control group there was a significant rise in mean DBP during intubation [94.33±5.22 (16.97 %)] , it remained above the baseline value till T10 [83.3±7.08(5.53%)] . There was a statistically significant difference in mean DBP across the groups. Srivastava VK et al [23] in 2015 found no significant increase in MAP comparative to baseline at any time intervals of intubation in group dexmedetomidine while increase was significant in group esmolol at 1, 2, and 3 min after intubation only ($P < 0.05$) . But with group control the comparison was statistically Significant ($P < 0.001$).

Rate Pressure Product, [(RPP) = Heart rate (PR) x Systolic Blood Pressure (SBP)] is a good estimate of myocardial oxygen requirement (Moon et al., 2012). RPP levels close to 20,000 are normally associated with angina and myocardial ischemia (Cokkinos and Voridis, 1976). Stone et al., 1988; Slogoff and Keats in 1989 demonstrated in their studies that when intraoperative heart rate increases above 110 beats min^{-1}, the incidence of myocardial infarction rises.According to the Mary's law, heart rate rises with the fall in blood pressure and vice versa; this phenomenon usually keeps the rate pressure product fairly constant. But any situation, which increases both heart rate and systolic blood pressure, the rate pressure product (RPP) is multiplied and hence it may cross the critical limit of ischemia. It has been proved that esmolol lowers RPP, which is a good predictor of myocardial oxygen consumption (MVO2).None of the patients in our study group showed heart rate > 110 beats min^{-1} (Table II) . S. Singh , E.F. Laing et al [24] in 2012 studied heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP) measured before induction as baseline, and at minute 1, 3 and 5 minutes respectively after tracheal intubation .They found significant attenuation in the experimental group as compared to the control group ($P < 0.05$) at 1 minute with onward decreases at 3 and 5 minutes respectively after intubation. However attenuation to baseline values at 5 minutes after intubation in the experimental group was significantly higher than that in the control group.Sharma S et al [25] in 2018 observed that three minutes after the completion of infusion of normal saline (NS) in control (C) group, dexmedetomidine in study group D, esmolol in study group E over 10 min, RPP increased from baseline 1 min after intubation in all the groups. RPP values in Group E were significantly lower than that of group C up to 7 min after intubation. In our study, the mean RPP in esmolol group was decreased during intubation (DI) by 4.31 % , at T1 it was reduced by 5.27% [9650.93± 1076.98]from the baseline value ,from T3 the RPP values started reaching near baseline value (1.95%) i.e., 3 min after intubation it remained around the baseline till T20 (2.7%). In control group the mean RPP was was increased by 53.39% during laryngoscopy and intubation (DI) above the baseline and remained 15.10% above the baseline value till T10.By T 15 the mean RPP reached near the baseline i.e 3.91 % and by T20 it was 4.34% from the baseline value. So the rise in mean RPP (53.39%) was highly significant in control group in comparison to esmlol group.

CONCLUSION

In conclusion, we recommend esmolol, an ultra short acting β blocker having half -life of 2.7-4.8 minutes, as the drug of choice for reducing the stress response of rise in HR, SBP and RPP during laryngoscopy and intubation. Besides, esmolol being a selective β blocker can be safely administered to patients with COPD and chronic smokers.

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LIMITATION

ASA physical status III and IV were not included who would have been affected more hemodynamically during laryngoscopy and intubation.

Serum levels of stress markers such as cortisol and catecholamine level during laryngoscopy and intubation could not be measured.

The premedication and the use of inhalational agent during induction of anesthesia may have influence in the study values during laryngoscopy and intubation.

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