A randomized controlled study of intravenous esmolol to attenuate the cardiovascular responses to laryngoscopy and endotracheal intubation

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INTRODUCTION

Laryngoscopy and endotracheal intubation are often accompanied with significant increases in heart rate and arterial blood pressure often leading to adverse outcome.¹ These responses are transient occurring 30 seconds after intubation and lasting less than 10 minutes.² The sympathoadrenal activation is also associated with dysrhythmias.³

Although these responses may be of short duration and of little consequence in healthy individuals, serious complications can occur in patients with underlying coronary artery disease reactive airways, or intracranial neuropathology.¹⁻⁶

These reflexes are mediated by the cardioaccelerator nerves and sympathetic system. This response includes wide-spread release of norepinephrine from adrenergic nerve terminals and secretion of epinephrine from the adrenal medulla.⁷

Esmolol is an ultra-short acting, beta-adrenergic receptor antagonist with efficacy to provide hemodynamic stability during laryngoscopy and tracheal intubation without side-effects.⁸ It inhibits Beta-1 receptors of myocardium thus attenuating positive chronotropic, to
very less extent it also inhibits Beta 2 receptors of smooth muscles of vascular walls thus attenuating positive inotropic effects.9

In this study, authors evaluate the effectiveness of Intravenous Esmolol in attenuating hemodynamic response to laryngoscopy and endotracheal intubation.

METHODS

Study period was May 2015 to May 2016. Study Population was 60 adult ASA grade I or II normotensive patients, undergoing elective surgery under general anaesthesia and willing to participate were the study population. Study design was it is a prospective randomized study. The approval for the study was obtained from the Institutional Ethics Committee.

Inclusion criteria

- Male and female of age group between 25 to 65 years. Undergoing elective surgery under general anesthesia. Weight 40 kg to 90kg. Resting systolic blood pressure less than 140 mmHg and diastolic pressure less than 90 mmHg. American Society of Anesthesiologist Grade I and II.

Exclusion criteria

- Ischemic heart diseases or ECG abnormalities indicating ischemic heart diseases. Patients with any overt cardiac, renal, pulmonary and liver diseases. Hypertensive patients. Any Patients with history of dyspnoea on exertion of grade III or more as per NYHA guidelines. Obesity (weight more than 90kg). Pregnancy. ASA grade III or IV patients. Anticipated difficult intubation. Any contraindication of Esmolol.

Pre-operative investigations and assessment

A preoperative evaluation was carried out in all patients with demographic data like age, gender, weight and detailed clinical history, physical examination including, associated medical co-morbidities, and current medications. Blood pressure was measured at three occasions at least 1 hour apart to confirm that it fulfils the selection criteria.

All routine and relevant investigations such as complete blood count, renal function test (serum electrolytes, serum creatinine, and blood urea levels), urine routine and microscopy, electrocardiogram, chest X-ray were carried out for all patients. The factors indicating difficult intubation on clinical examination were ruled out.

Pre-operative management

All patients received Tablet Pantoprazole 40 mg at night before surgery and 3 hours before surgery and Tablet Alprazolam 0.5 mg was given night before surgery. A 20G intravenous cannula was secured on non-dominant hand in appropriate vein in wards and intravenous fluid Ringers Lactate 500 ml as maintenance was started about 3 hours prior to surgery. About one hour prior to surgery, baseline readings were taken for pulse rate and blood pressures (Systolic, Diastolic and Mean) and were considered as preoperative baseline reading.

These patients were randomly allocated in to either group C (Control) or E (Esmolol). Once group was decided, blinding was not maintained.

In operation theatre

In the preoperative area, monitoring of hemodynamic parameters such as Heart Rate, Non-invasive blood pressure monitoring (NIBP), oxygen saturation (SpO2) and Electrocardiography (ECG) was done. Five ECG leads were placed on chest and Lead II, Lead aVL and Lead V were continuously observed on monitor. In operation theatre monitoring of these parameters were continued. All the 3 groups received sedation with Intravenous Midazolam 0.02 mg/kg and Fentanyl 2 mcg/kg about 15 minutes before induction. Preoxygenation with 100% oxygen by using facemask in closed circuit to achieve oxygen saturation (SpO2) of 98 - 99% was done.

- For Group ‘C’, patients were directly given inducing agent.
- For Group ‘E’, patients were given intravenous Esmolol 1.5 mg/kg 2 minutes before start of laryngoscopy.

Induction of anaesthesia was done with Intravenous Thiopentone 5mg/kg body weight given slowly till loss of eyelash reflex is seen. Then intravenous Succinylcholine was given in dose of 2 mg/kg.

Then facemask ventilation was done till twitches disappears and adequate relaxation obtained. Direct laryngoscopy was conducted by the same anaesthesia consultant for all cases, using standard McIntosh blade and an appropriate size cuffed endotracheal tube lubricated with non-anesthetic jelly and was inserted in single attempt and cuff will be immediately inflated with air to a pressure of 25 cm of water.

After confirming bilateral equality of air entry in lungs by auscultation, the endotracheal tube was secured with the adhesive tape. Ventilation was done by IPPV on ventilator. Ventilatory setting was set to provide tidal volume of 8-10 mg/kg and respiratory rate 14/minute for 10 minutes. No noxious stimulus or surgical incision was applied over 10 minutes after intubation. Supine position was maintained. Anaesthesia was maintained using 50% nitrous oxide and 50% oxygen with Isoflurane (MAC-1.0). Hemodynamic parameters were monitored as follows: Heart Rate (HR), Systolic Blood Pressure (SBP),
Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) by non-invasive technique.

The intervals for these measurements were

- Baseline (taken half an hour prior to anaesthesia)
- Before sedation
- After induction but before intubation
- Immediately after intubation
- Thereafter at 1, 2, 3, 4, 5 and 10 minutes.

After this monitoring for 10 minutes post-intubation, further operative and anesthetic procedure were continued as per plan.

**Statistical methods**

Statistical analysis was carried out with the help of SPSS (version 20) for Windows package (SPSS Science, Chicago, IL, USA). The description of the data was done in form of mean±SD for quantitative data while in the form of % proportion for qualitative (categorical) data. p-values of <0.05 will be considered significant.

For quantitative data, Unpaired Student’s t-test was used to test statistical significance of difference between two independent group means.

For comparison of categorical variables chi-square test was used.

**RESULTS**

Comparison of patient variables such as age, gender and weight show that there is no statistically significant demographical difference between group C and E. (Table 1).

Heart rate was lower in Group E as compared to Group C. There was no statistically significant difference at baseline, before sedation or after induction. Thereafter heart rate was statistically significant lower immediately after intubation till 4 minutes after intubation.

At 5 and 10 mins after intubation, heart rate was lower in group E but there was no statistically significant difference. (Table 2).

SBP was lower in Group E as compared to Group C. There was statistically significant lower SBP in Group E difference only immediately after intubation. At all other points of comparison there was no statistically significant difference (Table 3).

DBP was lower in Group E as compared to Group C. There was statistically significant lower DBP in Group E difference only immediately after intubation. At all other points of comparison there was no statistically significant difference (Table 4).

### Table 1: Comparison of patient variable.

| Variable | Groups | p value |
|----------|--------|---------|
|          | Group C (mean±sd) | Group E (mean±sd) |
| Age      | 36.03±9.219       | 37.6±12.653       | 0.5849 |
| Weight   | 60.8±10.965       | 63.93±7.856       | 0.2088 |
| Gender   | Male 20           | 19                |        |
|          | Female 10         | 11                | 0.786  |

### Table 2: Intergroup comparison of mean heart rate between group C and E.

|                   | Group C (mean±sd) | Group E (mean±sd) | p-value |
|-------------------|------------------|------------------|---------|
| Baseline          | 81.20±12.024     | 80.63±6.891      | 0.824   |
| Before sedation   | 84.60±11.171     | 81.60±7.233      | 0.232   |
| After induction   | 84.77±10.513     | 79.33±10.410     | 0.077   |
| Immediately after intubation | 101.60±11.935 | 88.67±7.747 | 0.000* |
| 1 min             | 99.10±11.514     | 88.77±8.016      | 0.000*  |
| 2 mins            | 96.10±11.400     | 87.53±7.519      | 0.002*  |
| 3 mins            | 93.73±11.453     | 86.53±7.615      | 0.009*  |
| 4 mins            | 90.13±11.658     | 84.37±7.308      | 0.034*  |
| 5 mins            | 85.93±11.310     | 82.73±7.759      | 0.222   |
| 10 mins           | 83.63±11.731     | 80.93±7.843      | 0.316   |

*statistically significant

### Table 3: Intergroup comparison of mean systolic blood pressure between group C and E.

|                   | Group C (mean ± sd) | Group E (mean ± sd) | p-value |
|-------------------|---------------------|---------------------|---------|
| Baseline          | 121.83±8.526        | 120.80±9.368        | 0.603   |
| Before sedation   | 125.37±8.704        | 119.93±9.584        | 0.220   |
| After induction   | 119.70±8.647        | 117.07±8.998        | 0.241   |
| Immediately after intubation | 161.90±11.929 | 155.07±12.086 | 0.008* |
| 1 min             | 151.10±10.114       | 150.73±10.696       | 0.877   |
| 2 mins            | 142.93±7.428        | 145.53±9.912        | 0.229   |
| 3 mins            | 137.67±7.950        | 141.00±9.040        | 0.104   |
| 4 mins            | 132.83±7.410        | 133.53±8.460        | 0.731   |
| 5 mins            | 127.90±8.168        | 126.27±9.752        | 0.460   |
| 10 mins           | 124.37±9.046        | 120.40±8.869        | 0.073   |

*statistically significant
Myocardial ischemia might occur during the induction-intubation sequence in patients with coronary artery disease. Intraoperative ischemia has been associated with a high rate of perioperative myocardial infarction.11 During procedure like direct laryngoscopy involving severe sympathetic stimuli prevention of tachycardia, hypertension and rise in total oxygen consumption may prove beneficial in patients with limited cardiac reserve.12

Esmolol is effective, in a dose-dependent manner, in the attenuation of the sympathomimetic response to laryngoscopy and intubation. Shrestha et al, noted that doses of Esmolol higher than 1.5 mg/kg did not completely prevent the pressor response to laryngoscopy and intubation. Sum et al, has also found a similar effect in addition to increase in intracranial pressure.13,14

Dyson et al, noted that Esmolol in doses 1 mg/kg was insufficient to control the increase in systolic blood pressure compared to 1.5 mg/kg and 2 mg/kg which controlled both systolic blood pressure and heart rate, but 2 mg/kg dose produced significant decreases in systolic blood pressure.15

Miller et al, in their study have reported that 100 mg of single bolus dose of Esmolol was effective for controlling the hemodynamic response to tracheal intubation in a Canadian multicenter trial.16

Study done by Sanjeev Singh et al, comparing Esmolol also showed significant increase in Heart Rate after intubation and remained significantly high at 3 and 5 mins.17 They also found increase in SBP, DBP and MAP from the baseline in after Esmolol at 1 min with decreases at 3 and 5 min respectively after intubation. In this study also authors found Heart rate well controlled with Esmolol bolus but Blood pressure remained was controlled only for a short duration.

Unlike this study, Liu et al, who used Esmolol infusion to control hemodynamic responses associated with intubation, found significant decreases in an SBP prior to induction and post-intubation, compared to the placebo group.18 This could be because in their study patients received infusion rather than bolus like this study.

In present study, pretreatment with Esmolol 1.5 mg/kg attenuated, but did not totally obtund, the cardiovascular response to tracheal intubation after induction of anesthesia and these findings are similar with previous studies.17 β-adrenoceptor blockade minimizes increase in HR and myocardial contractility by attenuating the positive chronotropic and inotropic effects of increased adrenergic activity. But it failed to effectively attenuate hypertensive response to intubation.

**DISCUSSION**

The hemodynamic response characterized by tachycardia and hypertension to manipulation in the area of the larynx, by means of laryngoscopy and intubation, is well-recognized. Stimulation of mechanoreceptors in the pharyngeal wall, epiglottis and vocal cords, is thought to be the cause for this hemodynamic response. Cardiovascular pressor response following laryngoscopy and tracheal intubation has been investigated extensively since these changes were initially reported.10

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**Table 4: Intergroup comparison of mean diastolic blood pressure between group C and E.**

|                | Group C (mean±sd) | Group E (mean±sd) | p-value  |
|----------------|-------------------|-------------------|----------|
| Baseline       | 78.50±6.073       | 76.93±4.927       | 0.449    |
| Before sedation| 77.40±6.306       | 76.83±4.745       | 0.775    |
| After induction| 74.47±6.241       | 74.43±11.352      | 0.404    |
| Immediately after intubation | 94.13±7.366 | 89.53±8.016 | 0.015* |
| 1 min          | 88.57±7.463       | 86.37±8.869       | 0.192    |
| 2 mins         | 86.57±6.590       | 84.23±9.591       | 0.174    |
| 3 mins         | 83.87±6.202       | 84.23±9.591       | 0.481    |
| 4 mins         | 82.40±6.344       | 80.63±9.608       | 0.319    |
| 5 mins         | 79.33±4.908       | 77.90±9.532       | 0.428    |
| 10 mins        | 77.27±5.382       | 73.80±8.919       | 0.051    |

*Statistically significant

**Table 5: Intergroup comparison of mean MAP between group C and E.**

|                | Group C (mean±sd) | Group E (mean±sd) | p-value  |
|----------------|-------------------|-------------------|----------|
| Baseline       | 90.90±8.057       | 91.53±6.485       | 0.749    |
| Before sedation| 91.63±7.695       | 89.50±6.431       | 0.226    |
| After induction| 86.27±7.755       | 86.27±6.787       | 1.000    |
| Immediately after intubation | 115.73±11.922 | 109.80±7.911 | 0.045* |
| 1 min          | 112.73±10.945     | 106.00±8.383      | 0.014*   |
| 2 mins         | 108.47±9.899      | 102.97±8.336      | 0.030*   |
| 3 mins         | 103.57±9.555      | 99.63±7.792       | 0.117    |
| 4 mins         | 99.93±8.706       | 97.00±7.297       | 0.183    |
| 5 mins         | 95.00±7.344       | 92.43±6.951       | 0.176    |
| 10 mins        | 90.93±7.148       | 88.57±7.055       | 0.226    |

*Statistically significant

**CONCLUSION**

In Normotensive patients requiring general anaesthesia with laryngoscopy and intubation, after induction with Fentanyl and Thiopentone, and Succinylcholine as muscle relaxant, authors found that intravenous Esmolol 1.5 mg/kg attenuated Heart rate response but fails to satisfactorily prevent rise in blood pressure.
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