# Potential Attenuating Effect of Single Bolus Dose of Esmolol on Cardiovascular Stress Response in Elective Neurosurgical Cases

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## Abstract

A prospective, double blind and randomized study was conducted in the Department of Anesthesiology of Dhaka Medical College Hospital, Dhaka, Bangladesh, between January 2013 and January 2014, to assess the efficacy of single bolus dose of esmolol (1.5mg/kg) to attenuate the cardiovascular stress response in elective neurosurgical cases. A total of 100 elective neurosurgical patients were enrolled in this study. Patients were randomly allocated equally into two groups: group A and group B, having 50 patients in each group. Patients of group A received intravenous esmolol (1.5mg/kg), 3 minutes before induction, while patients of group B received intravenous 10 ml of normal saline 3 minutes before induction. Parameters like heart rate, systolic and diastolic blood pressure were recorded before induction and every alternative minute for 10 minutes after endotracheal intubation. There were no differences in baseline demography of the patients (P>0.05). However, our data showed that in group A, there were significant reductions in heart rates immediately after induction, 1 minute, 3 minutes and 5 minutes after endotracheal intubation (P<0.01), as well as significant reductions in systolic and diastolic blood pressure after 1 minute, 3 minutes and 5 minutes of endotracheal intubation (P<0.01) respectively, in comparison to group B. Besides, reductions in rate pressure product were observed immediately after induction and 1 minute, 3 minutes and 5 minutes after endotracheal intubation respectively in group A, as compared to group B (P<0.01). In summary, a single bolus dose of esmolol (1.5mg/kg) effectively attenuates the cardiovascular stress response during and after laryngoscopy and endotracheal intubation in elective neurosurgical cases.

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## Introduction

Neurotrauma, anaesthesia, hypoxia and pain can make human body produce a stress response; it leads to severe metabolic and homeostasis disorders and immune suppression leading to massive release of hormones and increased blood sugar, causing serious physiological dysfunction.[1] Direct laryngoscopy and endotracheal intubation during anesthesia frequently induces a cardiovascular stress response characterized by hypertension and tachycardia due to reflex sympathetic stimulation.[2] The response is transient occurring within 30 seconds after intubation and lasting for less than 10 minutes.[2] It may be well tolerated in healthy people, but may be hazardous in patients with hypertension, coronary artery disease, cerebrovascular disease, myocardial infarction and thyrotoxicosis.[3] Tracheal intubation induces clinically relevant neuro-vegetative responses.[4-6] Plasma concentration of catecholamines is increased and myocardial ischaemia or cerebral hemorrhage may ensue.[3-7]

Many attempts have been made to modify those hemodynamic responses e.g. with beta blockers, antihypertensive agents like phentolamine, nitroglycerine, sodium nitroprusside and opioids; those were found effective but not free of hazards.[8-12] Beta blocker such as esmolol is effective in attenuating sympathetic responses to laryngoscopy and intubation.[13,14]

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Esmolol possesses some properties which makes it a valuable agent to obtund the cardiovascular response.[14] Firstly, it is a cardio selective agent. Secondly, it has ultrashort duration of action (9 minutes) and finally, significant drug interaction with commonly used anesthetics has not been reported.[15] However, no consensus has been reached regarding the optimum dose and timing of its delivery Esmolol is potentially safer to use than longer-acting antagonist in critically ill patient who require adrenoceptor antagonists.[14,16] Many studies were carried out to find out the effective dose of esmolol to attenuate the cardiovascular stress response in different countries; however, there is a scarcity of similar study in our country. [13-15,17-21] Besides, ethnic differences in effectivity of any drug is a specific interest for the researchers, as evidence suggest that African-Americans respond less well to beta adrenergic receptor blocking drugs as whites do.[22] Considering all those, we proposed this study to assess the efficacy of single bolus dose of esmolol (1.5 mg/kg) to attenuate the cardiovascular stress response in elective neurosurgical cases.

## Methods

This prospective, double blind and randomized study was conducted in the Department of Anesthesiology of Dhaka Medical College Hospital, Dhaka, Bangladesh, between January 2013 and January 2014. A total of 100 patients with ASA physical status I, II & III scheduled for various elective neurosurgical procedures under general anesthesia were enrolled in this study. Patients were divided into two equal groups according to the computerized random table: group A and group B, having 50 patients in each group. Group A received intravenous bolus esmolol (1.5mg/kg), while Group B received intravenous 10 ml of normal saline 3 minutes before induction. The treatment drugs were diluted in a coded syringe by an individual anesthesiologist who did not take part in induction of the patients. In the same way, observation and management of tachycardia and rise of blood pressure were carried out by another anesthesiologist who was unaware of the groups. On the operation table, a 20-gauge intravenous cannula was inserted into a suitable vein of either forearm or dorsum of the hand of the patient to secure the intravenous channel and ECG, NIBP & SpO2 monitors were applied. Baseline parameters, i.e. heart rate, systolic and diastolic blood pressure were noted before administration of the drugs used. After pre-oxygenation for 5 minutes, calculated doses of esmolol and normal saline (10ml) were given slowly in group A and group B respectively. Patients were induced with thiopental sodium (5mg/kg) one minute after receiving either esmolol or normal saline. Then succinylcholine (1.5mg/kg) was used to facilitate intubation. Fentanyl (1.5mg/kg) was given to both groups for analgesia. Anesthesia was maintained with nitrous oxide (65%) in oxygen and Isoflurane. Vecuronium bromide (0.1mg/kg) was given for maintenance of muscle relaxation. At the end of surgery, all patients were reversed with Neostigmine (0.05mg/kg) and atropine (0.02mg/kg). Parameters like heart rate, systolic and diastolic blood pressure were recorded in every alternate minute for 10 minutes after intubation.

Data were collected on a pre-designed data collection sheet and later compiled in a master chart. All data were presented as percentage and Mean±SD where applicable. Student's 't' test and chi-square test were used to difference in between two groups. P value <0.05 was accepted

as statistically significant. Statistical analysis was done using Statistical Package for Social Science (SPSS) for Windows version 17.0. The study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh.

## Results

Mean age of the participants were 38.2±12.5 years and 35.7±11.7 in group A and B respectively, while mean weight were 56.7±11.3 kg and 54.4±9.2 kg respectively. Male and female were 18(36%), 32(64%) and 21(42%), 29(58%) in group A and B respectively. The differences between the two groups are not statistically significant in terms of age, weight and sex (P>0.05) (Table-I). Comparison of heart rates is shown in table-II. No difference was found in heart rates between the two groups before induction (P>0.05). However, significant differences were observed immediately after induction, 1 minute, 3 minutes and 5 minutes of endotracheal intubation (P<0.01). Comparison of systolic blood pressure is shown in table-III. The difference in systolic blood pressure between the two groups before induction was statistically not significant (P>0.05). However, significant reductions were observed between two groups immediately after induction and after 1 minute, 3 minutes and 5 minutes of endotracheal intubation (P<0.01). Comparison of diastolic blood pressure is shown in table-IV. The difference in diastolic blood pressure between the two groups before induction was statistically not significant (P>0.05). However, significant reductions were observed between two groups immediately after induction and after 1 minute, 3 minutes and 5 minutes of endotracheal intubation (P<0.01). Comparison of rate pressure product is shown in table-V. No difference was found in rate pressure product between two groups before and immediately after induction (P>0.05). However, significant differences were observed between two groups after 1 minute, 3 minutes and 5 minutes of endotracheal intubation (P<0.01).

**Table-I:** Demographic characteristics of the patients (n=100)

| **Variables** | **Group A** (n=50) | | **Group B** (n=50) | | **P value** |
|---|---|---|---|---|---|
| Sex | Male | Female | Male | Female | >0.05 |
| | 18 (36%) | 32 (64%) | 21 (42%) | 29 (58%) | |
| Age (years) | 38.2±12.5 | | 35.7±11.7 | | |
| Weight (kg) | 56.7±11.3 | | 54.4±9.2 | | |

Parentheses indicate corresponding percentage. P-value reached from Chi-square test and unpaired Student's-t test respectively.

**Table-II:** Comparison of mean heart rate between two groups

| | **Group A** | **Group B** | **P value** |
|---|---|---|---|
| Before induction | 90.8±10.77 | 89.06±9.66 | >0.05 |
| Immediately after induction | 90.08±11.47 | 100.64±11.6 | <0.01 |
| 1 min. after intubation | 92.2±12.26 | 116.12±12.73 | <0.01 |
| 3 min. after intubation | 91.4±11.72 | 109.48±11.6 | <0.01 |
| 5 min. after intubation | 88.14±10.8 | 98.12±10.44 | <0.01 |

All values are expressed as Mean±SD. P value reached from unpaired Student's-t test.

**Table-III:** Comparison of systolic blood pressure between two groups

| | **Group A** | **Group B** | **P value** |
|---|---|---|---|
| Before induction | 125.8±7.26 | 126.48±7.28 | >0.05 |
| Immediately after induction | 118.56±8.59 | 112.84±9.34 | <0.01 |
| 1 min. after intubation | 125.6±11.32 | 159.08±8.58 | <0.01 |
| 3 min. after intubation | 124.88±10.79 | 148.48±8.76 | <0.01 |
| 5 min. after intubation | 122.24±7.12 | 136.92±7.51 | <0.01 |

All values are expressed as Mean±SD. P value reached from unpaired Student's-t test.

**Table-IV:** Comparison of diastolic blood pressure between two groups

| | Group A | Group B | P value |
|---|---|---|---|
| Before induction | 79.64±6.4 | 79.96±6.4 | >0.05 |
| Immediately after induction | 76.08±5.58 | 71.54±7.5 | <0.01 |
| 1 min. after intubation | 80.68±7.84 | 104.76±6.88 | <0.01 |
| 3 min. after intubation | 79.76±7.62 | 98.12±6.71 | <0.01 |
| 5 min. after intubation | 77.88±5.7 | 89.36±5.13 | <0.01 |

All values are expressed as Mean±SD. P value reached from unpaired Student's-t test.

**Table-V:** Comparison of rate pressure product between two groups

| | Group A | Group B | P value |
|---|---|---|---|
| Before induction | 11445.68 ±1685.87 | 11242.96 ±1173.69 | >0.05 |
| Immediately after induction | 10702.24 ±1745.21 | 11322.64 ±1336.9 | >0.05 |
| 1 min. after intubation | 11649.68 ±2223.18 | 18462.32 ±2163.14 | <0.01 |
| 3 min. after intubation | 11477.52 ±2122.12 | 16229.84 ±1735.46 | <0.01 |
| 5 min. after intubation | 10787.12 ±1564.65 | 13423.36 ±1522.34 | <0.01 |

All values are expressed as Mean±SD. P value reached from unpaired Student's-t test.

## Discussion

Direct laryngoscopy and tracheal intubation cause increased heart rate and blood pressure.[2] Mechanism of cardiovascular response to intubation is assumed to be a reflex sympathetic reaction to the mechanical stimulation of larynx and trachea.[17,18] Reflex changes in the cardiovascular system after laryngoscopy and intubation lead to an average increase in blood pressure by 40-50% and 20% increase in heart rate.[23] Significant elevations in serum levels of norepinephrine and epinephrine following laryngoscopy, with and without tracheal intubation, have been demonstrated.[2,3,23] We compared the hemodynamic changes in response to laryngoscopy and endotracheal intubation following induction of anesthesia using either esmolol (1.5mg/kg) or normal saline (0.9% sodium chloride solution). Comparing between the two groups, we found marked decrease in heart rates, systolic and diastolic blood pressure as well as rate pressure product after intubation is done.

Ghaus *et al.*[19] studied the effect of esmolol infusion in patients who received an infusion of either esmolol or 5% dextrose during laryngoscopy and intubation and found that esmolol is effective in attenuating the hemodynamic response during laryngoscopy and endotracheal intubation. However, the total dose of esmolol was much more than that of our study. Gupta *et al.*[24] compared the effectiveness of intravenous esmolol and lignocaine and reported that esmolol (1.5mg/kg) had better attenuation of stress response than lidocaine (1.5mg/kg). Their findings are in congruence with our findings as well as that of Begum *et al.*, Rajbhandari.[20,25] Feng *et al.*[26] reported that only esmolol could reliably offered the desired protection, while low dose of fentanyl (3micrograms/kg) prevented hypertension but not tachycardia, and 2mg/kg lidocaine had no effect to blunt adverse hemodynamic responses. Their results are supported by the findings of Islam *et al.*, Feng *et al.*, Ugur *et al.* – all of those findings are in congruence with our study results.[21,26,27]

In contrast, Korpinen *et al.*[28] reported that intravenous administration of esmolol 2mg/kg 2 minutes before laryngoscopy and intubation suppressed the increase in heart rates but not in arterial blood pressures and Tariq *et al.*[29] administered esmolol 1mg/kg on their study

subjects and concluded that esmolol partially attenuated the hemodynamic response but could not abolish it completely. This incomplete abolition of hemodynamic response is probably due to reduced dose of esmolol, as in most studies esmolol (1.5mg/kg) satisfactorily diminish the hemodynamic responses. We used esmolol (1.5mg/kg) and it could effectively decrease both heart rates and blood pressure. Moreover, Efe *et al*.[30] studied hemodynamic response of laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft surgery (CABG) on 45 randomized patients and reported that esmolol infusion is more effective than esmolol bolus administration in patients under anesthesia.

## Conclusion

In summary, a single bolus dose of esmolol (1.5mg/kg) effectively attenuates the cardiovascular stress response during laryngoscopy and endotracheal intubation in selective neurosurgical cases. Further studies with larger samples, longer duration, and at multiple sites are recommended.

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