

## Attenuation of cardiovascular response to laryngoscopy and tracheal intubation by a bolus dose of inj. esmolol and placebo – A comparative study

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Received: 02<sup>nd</sup> June, 2017

Accepted: 23<sup>rd</sup> July, 2017

### Abstract

**Introduction and Objectives:** Laryngoscopy and tracheal intubation are noxious stimuli that produce marked sympathetic responses manifesting as tachycardia and hypertension, which can be deleterious in susceptible-patients if they precipitate myocardial ischaemia, infarction, arrhythmias etc. Since  $\beta$ -blockers counteract these sympathetic activation, this clinical study was designed to evaluate and compare a short-acting  $\beta$ -blocker, Esmolol as IV bolus to a placebo in attenuating sympathetic responses at laryngoscopy and intubation in healthy adults.

**Materials and Methods:** This was a randomized prospective controlled study consisting of 60 patients who were allocated into group A (Esmolol) and Group B (Placebo). Patients were premedicated with glycopyrolate 0.2 mg IV 90 minutes before surgery. Esmolol was given as 100 mg IV bolus immediately before induction with Thiopentone 5 mg/kg and Suxamethonium 1.5 mg/kg. The study period extended up to 5 minutes after intubation. Pre-induction readings of Heart rate, Systolic blood pressure, Diastolic blood pressure, mean arterial pressure and Rate pressure product were compared to those at 1<sup>st</sup>, 3<sup>rd</sup> and 5<sup>th</sup> minutes after intubation. Changes in ECG and any other adverse effects were looked for.

**Results:** The mean values of Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure and Rate pressure product for esmolol group at pre-induction, at 1<sup>st</sup>, 3<sup>rd</sup> and 5<sup>th</sup> minute were noted to be as follows: (Figures in parenthesis for placebo).

Heart rate (b/min) was 87.93 (86.03), 87.37 (102.03), 88.40 (100.77), 88.13 (98.63); Systolic blood pressure (mmHg) was 130.93 (128.33), 128.80 (145.73), 122.80 (136.13), 121.80 (130.80); Diastolic blood pressure (mmHg) 81.40 (79.87), 79.00 (97.87), 78.07 (87.80), 78.67 (85.13); Mean arterial pressure (mmHg) was 97.35 (94.91), 94.03 (114.42), 93.01 (103.84), 92.68 (100.57) and Rate pressure product was 11323.60 (11042.50), 10831.6 (14971.4), 10826.8 (13817.9), 10779.9 (12896.6) respectively. There were neither significant adverse effects nor ECG changes.

**Interpretation and Conclusion:** Esmolol 100 mg IV bolus effectively attenuates sympathetic responses at laryngoscopy and tracheal intubation without any adverse effects.

**Keywords:** Diastolic blood pressure, Esmolol, Heart rate, Laryngoscopy and Tracheal Intubation (LTI), Mean arterial pressure, Rate pressure product, Systolic blood pressure.

### Introduction

Laryngoscopy and tracheal intubation are noxious stimuli that produce marked sympathetic response manifesting as tachycardia and hypertension. These haemodynamic changes are generally transitory and without sequelae. However in patients with preexisting coronary artery disease, hypertension and cerebrovascular disease, an increase in these circulatory parameters may precipitate myocardial ischaemia, arrhythmias, infarction and even cerebral haemorrhage.

Circulatory responses to laryngeal and tracheal stimulation were known since 1940 (Reid and Brace).<sup>1</sup> The study by Tomori and Widdicombe 1969, showed that mechanical stimulation of the respiratory tract caused increased nervous system activity in cervical sympathetic efferent fibres.<sup>2</sup>

These haemodynamic changes stem from reflex sympathetic discharge resulting from epi-pharyngeal and laryngopharyngeal stimulation associated with increased plasma norepinephrine concentrations.

Hence, to overcome this undesired response, the quest for an effective blockade of these responses has included the use of (Ebert and Pierson):<sup>3</sup>

- i. Premedication
- ii. Topical and systemic lidocaine
- iii. Vasodilators e.g. Isosorbide dinitrate, sodium nitroprusside
- iv.  $\alpha$  and  $\beta$  adrenergic blocking agents
- v. Angiotensin - converting enzyme inhibitors
- vi. Opiates e.g. Fentanyl, Alfentanil
- vii. Inhaled anaesthetic agents
- viii. Thoracic epidural block.

In appropriate doses, narcotics like fentanyl control both HR and BP responses, however complex respiratory depression and truncal rigidity are frequent accompaniments. Vasodilators and lidocaine provide an incomplete solution controlling hypertension, but having no effect on heart rate. Inhaled anesthetic agents also do not have encouraging effects in attenuating the haemodynamic response to Laryngo tracheal intubation

(LTI).

Since tachycardia appears to be associated more frequently with myocardial ischaemia than does hypertension, interesting approach towards attenuating cardiac responses to laryngeal stimulation, is the use of  $\beta$ -adrenergic antagonists. However attenuation of pressor response to LTI is desirable, excessive negative chronotropic and inotropic action of the  $\beta$ -receptor blockers may reduce coronary perfusion and precipitate heart failure in susceptible patients.

Among the  $\beta$ -adrenergic antagonists Esmolol (Methyl 3-4-(2-hydroxy-3- (isopropyl amino) propoxy-phenyl) propionate hydrochloride) has been an effective option because of its  $\beta$ -1 (cardioselective) adrenergic receptor blocking properties and its ultra-short duration of action. It has  $\alpha$ -distribution half-life of 2 min;  $\beta$ -elimination half- life of 9 min)

With Esmolol treatment, the difficulties of therapy with long lasting  $\beta$ -blockers are avoided. Sympathetic nervous system responses can be suppressed with a single dose i.v before tracheal intubation. In view of its pharmacokinetic profile, rapid onset, short elimination half-life and titrability, this study aims to evaluate the usefulness of Esmolol to deal with sympathetic activation at laryngoscopy and intubation.

This clinical study is designed to evaluate and compare intravenous Esmolol in a bolus dose to a placebo regarding:

- i. Haemodynamic responses to laryngoscopy and endotracheal intubation.
- ii. Effect on ECG (arrhythmias)
- iii. Any side effects

### Materials and Methods

Hospital ethics committee clearance was obtained for this study, Informed consent was taken from all the patients. They were posted for general anaesthesia from Departments of General Surgery, Orthopaedics, Obstetrics, Gynaecological and ENT.

### Study Design

This was a randomized prospective control study consisting of 60 normotensive patients who were allocated into two groups A and B, consisting of 30 each.

Group A (Esmolol)

Group B (Control)

### Inclusion criteria

- i. ASA grade I and II
- ii. Age 20 to 60 years.
- iii. Normotensive patients.

### Exclusion criteria

- i. Pulse rate <60 beats/min, hypertensive patients.
- ii. History of myocardial infarction in the past 6 months.
- iii. Conduction abnormality in ECG.
- iv. Patients predicted to have difficult intubation like

short neck, large tongue, and high arched palate.

- v. Paediatric patients.
- vi. Clinically significant hepatic renal and metabolic dysfunction.

Patients satisfying the above said inclusion and exclusion criteria were subjected to the study. They were randomly allocated into two groups A and B. Intravenous cannulation was secured. All patients were premedicated with injection glycopyrrolate 0.2 mg IV. Non-invasive blood pressure monitor, pulse oximeter probe and ECG were connected. Baseline readings of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and ECG were recorded.

All patients were pre-oxygenated for 3 minutes with 100% oxygen. Group A patients received Esmolol 100 mg IV bolus slowly over 15 seconds, whereas in group B 10 ml saline was given as placebo. This was soon followed in both the groups by induction with IV Thiopentone sodium 5 mg/kg (2.5%) and Suxamethonium chloride 1.5 mg/kg and ventilated with 100% oxygen. Laryngoscopy and intubation was done within 60 seconds.

Subsequently anaesthesia was maintained by IPPV with oxygen, nitrous oxide, halothane, delivered through closed circuit with circle absorber. Muscle relaxation for the contemplated surgery was provided by vecuronium. Patients were extubated after reversal at the end of the procedure on stable parameters.

The present study focussed on events from the time of injection of the study drug/placebo upto 5 minutes after intubation. Surgery was carried out only after the study period. Analgesics and other adjuvants were also administered after this period. Precurarization was not undertaken in the whole series.

The following parameters were observed:

1. Baseline readings (pre-induction) of heart rate, systolic, diastolic, mean arterial blood pressure and rate pressure product.
2. Reading of the above said parameters at 1, 3, and 5<sup>th</sup> minute after intubation.
3. Continuous ECG monitoring for arrhythmias, ST changes.
4. Adverse effects namely burning on injection, bronchospasm, and postoperative phlebitis.

The results of the study are analyzed, tabulated and subjected to statistical analysis. Inter-group and intra-group variations were compared using Chi-square test, Fischer Exact test and student "t" test. A p value of <0.05 was considered as significant.

### Results

The mean age of Esmolol group is 28.97±4.64 years and in the control group is 28.30±6.36 years. The mean weight of Esmolol group is 60.33±11.06kgs and for the control group is 61.50± 11.24 kgs. The

differences of these means are not statistically significant. Sex distribution between the two groups is statistically similar.

Types of procedures commonly carried out in Esmolol group are laparoscopic appendectomy and

LTO, and in the control group, the commonly carried out procedures are LTO and laparotomy. The baseline parameters between the two groups are statistically similar ( $p>0.05$ ) and clinically no difference is observed. (Table 1)

**Table 1: Baseline parameters**

Baseline	Mean + SD		p value
	(Min-Max)		
	Esinolol group	Control group	
Heart rate (beats/min)	87.93±4.35 (78-94)	86.03±5.24 (74-94)	0.139
Systolic Blood Pressure (mmHg)	130.93±10.84 (120-180)	128.33±6.01 (110-140)	0.255
Diastolic Blood Pressure (mmHg)	81.40±7.67 (70-90)	79.87±5.65 (70-90)	0.381
Mean Arterial Pressure (mmHg)	97.35±6.01 (86.66-106.66)	94.91±8.21 (85.67-105.33)	0.194
Rate Pressure Product	11323.60±752.15 (9360-12596)	11042.50±925.93 (8360-12480)	0.202

Heart rate did not change significantly during the study period in Esmolol group. In absolute values, there is negligible change in heart rate in Esmolol group throughout, whereas in control group, the change in heart rate has been from 86.03±5.24 to 102.03±4.77 at 1<sup>st</sup> minute, and 100.77±3.54 at 3<sup>rd</sup> minute. Heart rate was stabilized in the study period in Esmolol group. The percentage of change in Esmolol group is restricted to only 3.4%, whereas in the control group it was 77.7% as observed by effect size of partial Eta square and is statistically significant. (Table 2).

**Table 2: Changes in heart rate**

Recorded timing	Mean heart rate (b/min)±SD (Min-Max)		p value
	Esmolol group	Control group	
Baseline	87.93±4.35 (78-94)	86.03±5.24 (74-94)	0.139
1 <sup>st</sup> minute after intubation	87.37±9.47 (78-94)	102.03±4.77 (88-112)	p<0.001
3 <sup>rd</sup> minute after intubation	88.40±3.12 (78-94)	100.77±3.54 (94-110)	p<0.001
5 <sup>th</sup> minute after intubation	88.13 ± 1.81 (86-92)	98.63 ± 2.44 (94-104)	p<0.001
Significance	F=1.021 p=0.387	F=101.29 p<0.001	-
Estimate of effect size	0.034	0.777	-

The significant change of mean arterial pressure is noticed in both Esmolol and control group. The change is only 22.5% in the Esmolol group and is 66.5% in control group. Esmolol group has less variation in mean arterial pressure. (Table 3).

**Table 3: Changes in Mean Arterial Pressure (mmHg)**

Recorded timings	Mean MAP±SD (Min-Max)		p value
	Esmolol group	Control group	
Baseline	97.35±6.01 (86.66-106.66)	94.91±8.21 (85.67-105.33)	0.194
1 <sup>st</sup> minute after intubation	94.03±3.93 (86-103.33)	114.42±4.97 (106.66-133.33)	p<0.001
3 <sup>rd</sup> minute after intubation	93.01±4.34 (86.33-103.33)	103.84±5.97 (89.33-116.66)	p<0.001

5 <sup>th</sup> minute after intubation	92.68±4.29 (83.33-103.33)	100.57±5.63 (86.66-110.66)	p<0.001
Significance	F=8.420 p<0.001	F=57.046 p<0.001	-
Estimate of effect size	0.225	0.663	-

Rate pressure product has significantly changed in both the groups during the study period. The change in Esmolol group is 27.2% and in control is 81.2%. Esmolol group has less variation in rate pressure product. (Table 4).

**Table 4: Changes in Rate Pressure Product**

Recorded timings	Mean RPP±SD (Min-Max)		p value
	Esmolol group	Control group	
Baseline	11323.60±752.15 (9360-12596)	11042.50±925.93 (8360-12480)	0.202
1 <sup>st</sup> minute after	10831.6±876.01	14971.4±1341.88	p<0.001
3 <sup>rd</sup> minute after intubation	10826.8±746.10	13817.9±848.52	p<0.001
5 <sup>th</sup> minute after intubation	10779.9±577.71	12896.6±809.35	p<0.001
Significance	F=10.811 p<0.001	F= 130.620 p<0.001	-

## Discussion

Circulatory disturbances are reflexly provoked by sympathetic stimulation during laryngoscopy and tracheal intubation, which is associated with rise in plasma norepinephrine.<sup>4</sup> These changes are marked by increase in blood pressure and heart rate and occasionally arrhythmias. Less commonly bradycardia may occur as a result of vagal stimulation.<sup>5</sup> There is a potential for life threatening complications due to these changes in patients with CAD, systemic arterial hypertension, aneurysmal vascular disease and decreased intracranial vascular compliance, due to myocardial ischaemia, heart failure and cerebrovascular catastrophies.<sup>6-9</sup>

Strategies to circumvent these changes have included minimizing the duration of laryngoscopy, IV narcotics, IV or topical lidocaine, vasodilators, long action beta - blocking agents, inhaled anaesthetics, thoracic epidural analgesia.<sup>3,4,10</sup>

However none of these techniques are foolproof, hence in this context an attractive option is a relatively new  $\beta$ -blocking agent Esmolol, which we have investigated in our series.

The desirable properties of Esmolol are its short duration of action, cardioselective beta-adrenergic receptors blocking properties, its eliminative half-life of 9 min, non-irritating to veins and minimal or no side effects.

We chose to evaluate Esmolol in healthy subjects (ASA 1 and II). Though ASA class III and IV have been excluded, it is clear that the circulatory changes due to LTI could obviously be harmful in the setting of CAD and rise in ICP. There are studies to show usefulness of  $\beta$  blockers in such patients. It is known that the effect on heart rate after Esmolol bolus dose

comes on at 1 min, whereas the effect of BP comes after 2 min Figueredo et al (2001).<sup>10</sup>

Ebert et al<sup>3</sup> 1989 observed that maximum cardiovascular response occurred 2 min after intubation. They also noted that the responses (hypertension, tachycardia) are proportional to the duration of laryngoscopy. They recommend that the duration of LTI should be limited to 30 sec. In this context, we can expect severe reflex response during difficult or prolonged intubation, where Esmolol infusion is probably best preferred. In our study, we did not have cases of difficult intubation and we compared the pre-induction reading to parameters at 1, 3 and 5 min after intubation. LTI was done at 2 min after injection of study drug. We have noticed that Esmolol-induced attenuation extended throughout the 5 minutes of study period.

The advantages of bolus method are convenience, ease of administration, quick execution and no additional equipment. We employed in our series only bolus dose 100 mg by virtue of simplicity, rapidity and convenience. Figueredo et al<sup>10</sup> states the aim of optimum dose and mode of administration is to produce maximum attenuation postlaryngoscopy but minimum changes post-intubation.

Comparison of results of various studies is hampered by various factors like non-uniformity of patient's population, premedication, use of induction agents. The other factors are concomitant use of opiates, relaxants and co-induction agents. The doses of Esmolol and the rate of injection and also the time sequence in the administration of all the concerned drugs at induction are variable.

Causes of tachycardia may be traced to fear, anxiety, Suxamethonium and prolonged laryngoscopy

Ebert, Pierson et al (1989)<sup>3</sup>. Tachycardia more than 20% of baseline has potential to reduce myocardial perfusion. In the study conducted by Miller,<sup>12</sup> Sheppard<sup>4</sup> and Korpinen,<sup>13</sup> Esmolol produced fall in heart rate in all. But did not avoid rise in blood pressure. Oxorn et al<sup>14</sup> also noted in 100 mg and 200 mg doses reduction in heart rate upto 2.5 min only after intubation, but no effect on blood pressure.

Ebert, Pierson et al<sup>3</sup> made an interesting

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**Table 5**

Variables	Shane Sheppard et al <sup>4</sup>	Vucevic et al <sup>15</sup>	Ghaus et al <sup>5</sup>	Miller et al <sup>12</sup>	Our study
Heart rate (b/min)	79-85	79 – 92	90-91	69-74	87-88
SBP (mmHg)	140 - 147	133-151	125-124	-	130-121
DBP (mmHg)	-	-	79-79	-	81 -78
MAP (mmHg)	-	-	95.03 -94.8	103-107	97.35-93.01
RPP (x 10 <sup>3</sup> )		..	-	11.4-9.2	11.32-10.77

Rate pressure product is a useful index of myocardial demand. Esmolol in a dose of 3 mg/kg profoundly reduced the rate pressure product to  $9.2 \pm 3.8 \times 10^3$ , whereas 1.5 mg/kg Esmolol simply attenuated only heart rate and mean blood pressure response (Miller et al).<sup>12</sup> Rate pressure product above 15000 is undesirable in patients with CAD (Vucevic).<sup>15</sup> He found rate pressure product was at 15000 in most of control group patients and in the Esmolol group, it was less than 15000. Ebert, Pierson et al (1989) in their series on ASA grade III and IV found a rise in rate pressure product upto 50% in placebo group compared to only 20% rise in Esmolol group. In our series, there was a fall in rate pressure product by 4.3% below baseline in Esmolol group whereas in control group there was rise by 25%.

Donald Oxorn et al,<sup>14</sup> in his study found that Esmolol reduced the incidence of ventricular arrhythmias. Korpinen et al<sup>13</sup> did not encounter cardiac arrhythmias in both Esmolol and placebo group. Results of our study are in agreement with the above said.

Vucevic et al (1992)<sup>15</sup> reported that the only side effect of Esmolol is phlebitis, which can be avoided by suitable dilution. No side effects have been noticed with bolus doses in Donald Oxorn (1990)<sup>14</sup> and -Shane Sheppard (1990)<sup>4</sup> study. In our series too we did not see any side effects.

### Conclusion

It is concluded that Esmolol in a bolus dose of 100 mg IV given at induction of general anaesthesia

1. Effectively attenuates HR response to laryngoscopy and intubation.
2. Prevents hypertensive response to laryngoscopy and intubation.
3. Produces the net effect of favourable RPP, which may be beneficial to myocardial perfusion.

observation in ASA grade III. They noted decrease in systolic blood pressure and heart rate while diastolic blood pressure was maintained in patients given Esmolol as infusion. They theorized that this could maintain good myocardial perfusion.

The table 5 below shows the changes in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product of different authors as compared to our study.

4. Does not cause ischaemic changes in ECG.
5. These effects last for atleast 5 minutes after administration.
6. The above said effects occur in healthy subjects (ASA I and II) without concomitant administration of opiates, sedatives (or) inhalational anaesthetics.
7. No serious adverse effects such as bronchospasm, hypotension, bradycardia, conduction blocks and phlebitis are encountered.

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