

## Attenuation of hypertensive response with esmolol and labetalol in low doses in orotracheal intubation: A comparative study

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### Abstract

**Introduction:** This was a prospective, randomized, double blind, comparative, clinical study to assess the efficacy of Esmolol and Labetalol, in low doses, for attenuation of sympathomimetic response to laryngoscopy and intubation.

**Materials and Methods:** This study was conducted on 50 ASA 1 patients of either sex undergoing elective surgeries under general anaesthesia. Patients were randomized into two groups; group E who received intravenous Esmolol (0.5 mg/kg) or group L who received intravenous Labetalol (0.25 mg /kg) prior to induction and hemodynamic parameters were recorded as per designed protocol to assess stress response to laryngoscopy and intubation.

**Results:** Both the study groups had similar demographic profile. Instat version 3.10 was used for statistical calculations. The study data were analyzed using statistical methods of mean, standard deviation. Esmolol (0.5 mg/kg), abetalol (0.25 mg/kg) significantly attenuated the rise in heart rate, systolic blood pressure, and RPP during laryngoscopy and intubation. However, the difference was not statistically significant among the values for DBP and MAP.

**Conclusion:** From our clinical study it can be concluded that in lower doses, intravenous Labetalol (0.25 mg/kg) is a better agent than intravenous Esmolol (0.5 mg/kg) in attenuating the sympathomimetic response to laryngoscopy and intubation. Usual dose of esmolol used to obtund intubation response is 2-4mg/kg, while labetalol has been tried in all doses ranging from 0.25, 0.5, 0.75, and 1 mg/kg.<sup>17</sup>

**Keywords:** Esmolol, Labetalol, Stress response, Laryngoscopy and Intubation.

### Introduction

Despite the emergence of new airway devices in the recent years, rigid laryngoscopy and tracheal intubation still remains the gold standard in airway management. The major conditions in which the hemodynamic changes may pose serious challenges are cardiovascular diseases like hypertension, coronary artery disease, vascular aneurysms. Sudden hemodynamic changes may lead to left ventricular failure and myocardial ischemia in these patients. Those with decreased intracranial compliance and increased intracranial pressure like intracranial tumors or cerebral hematomas may collapse due to cerebral hemorrhage. Circulatory effects of laryngoscopy and intubation like reflex tachycardia and hypertension are marked in many patients.<sup>1</sup> Cardiovascular response to laryngoscopy and intubation is a reflex phenomenon with afferent stimuli carried by Glossopharyngeal nerve and Vagal pathways which activate suprasegmental and hypothalamic sympathetic centers to cause peripheral sympathoadrenal responses with release of Adrenaline and Noradrenaline.<sup>2</sup> Blood pressure elevation is due to Norepinephrine whereas changes in heart rate are Epinephrine related.<sup>2</sup> Beta blockers with bradycardiac, antihypertensive, antiarrhythmic and antiischemic properties are found to have role in preventing cardiovascular stress response to intubation.

This reflex hemodynamic changes are better tolerated in health, but they are greatly exaggerated and detrimental in patients with comorbidities.<sup>1</sup> Various pharmacological attempts have been made to obtund the pressor response. Volatile inhalational agents, intravenous Lignocaine, intravenous Opioids like Fentanyl, Alfentanil, Remifentanil, vasodilators like Sodium Nitroprusside, Nitroglycerine, calcium channel blockers like Verapamil, Diltiazem and adrenergic blockers like Clonidine are widely used. Several studies on intravenous Esmolol and intravenous Labetalol given preoperatively showed effectiveness in decreasing stress response. Esmolol is a cardio selective  $\beta_1$ -blocker having rapid onset and short duration of action. It causes depressor effect on myocardium; therefore, its place still remains to be defined especially in cardiac risk patients. Labetalol, an  $\alpha$  and  $\beta$  blocker, has also been found to be useful in preventing perioperative undesirable cardiovascular events but in higher doses, it may cause hypotension and bradycardia. With this background we conducted a prospective, randomized, double blind, comparative clinical study of low dose Esmolol versus low dose Labetalol with aims and objectives to study efficacy in preventing stress response to laryngoscopy and intubation and to study various hemodynamic parameters intraoperatively and to study any side effects.

## Materials and Methods

After getting approval from the institutional ethical committee, a prospective, randomized, double blind study was conducted on 60 ASA 1 patients (30 in each group) of either sex undergoing elective surgeries under general anaesthesia in Orthopedic operation theatre over a period of one year. This was a pilot study with Confidence: 0.95, Probability: 0.05 so the calculated sample size was 59. We took a rounded figure of 60. This implied that problems with a prevalence of 5% will almost certainly be identified (with 98% confidence) in a pilot study including 59 patients. ASA 1 & 2 patients of either sex between age group of 20-50 yrs having height between 150-180 centimeters and weight between 50-70 kilograms were included in the study. Patients with extremes of age, or known asthmatic, COPD patients, those having baseline bradycardia or heart block, or on beta blockers were excluded from the study.

Blinding was done using the SNOSE (sequentially numbered opaque sealed envelope) technique. Patients were allocated to any of the two groups-

Group E (Esmolol), Group L (Labetalol) respectively. After confirming nil per oral status and following informed consent, peripheral line was secured with 18 G Veinlon and intravenous fluid Ringers lactate was started. Monitors like Non Invasive Blood Pressure monitor, Electrocardiography leads and pulse oximeter were connected. Group E (Esmolol) received 0.5 mg/kg diluted with 0.9% saline to 10 ml intravenously 3 min prior to intubation. Group L (Labetalol) received 0.25 mg/kg diluted with 0.9% saline to 10ml intravenously 3 min prior to intubation as per randomization. Along with study drug all patients received premedication with injection Midazolam 0.02mg/kg, injection fentanyl [2µg/kg] was given 5 minutes before induction. Preoxygenation with 100% Oxygen for 3 minutes was done. All patients were induced with injection Thiopentone 5mg/kg intravenously and relaxation achieved by injection Vecuronium 1mg/kg intravenously after confirmation of mask ventilation. All intubation were done by well experienced anaesthetist and the same doctor did all the cases to minimize bias. Intraoperatively anaesthesia was maintained by O<sub>2</sub>: N<sub>2</sub>O (1:1) with Isoflurane upto 1.5%. Muscle relaxation was achieved with injection Vecuronium 0.2mg/kg.

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) Mean arterial pressure (MAP), Rate pressure product (RPP) was measured preinduction, at intubation and at 1,3,5,10 min post induction by another anaesthetist who was blinded to the study. For statistical analysis heart rate & Blood Pressure changes  $\pm 30\%$  was considered significant. Statistical analysis was performed using the INSTAT software version 3.10. The study data were analyzed using statistical methods of mean, standard deviation, paired students "t" test (for values within the group at different time stations) and independent samples "t" test (for comparison of intergroup values). A p value < 0.05 was considered significant and < 0.01 highly significant.

## Observation and Result

Data was collected in master chart and statistical analysis was done. Demographically both groups were similar and there was no significant difference. Duration of surgery was similar in both groups with P value of 0.8 suggesting that same type of cases were included in the study. Cases were done by an experienced anaesthetist and all intubations were performed by the same person to minimize bias and were done in almost same time of 11-13 sec in both the groups. Both groups had similar pulse rates before induction but at intubation and 1, 3,5,10 min post intubation there was significant difference (P Value < 0.05) with Labetalol group having lower pulse rates at all times thus achieving better control than Esmolol. Systolic blood pressure between two groups remained same before intubation but at intubation and 1, 3, 5, 10 min following intubation results were in favor of Labetalol group which had lower values as compared to Esmolol group (P Value < 0.05). On the other hand diastolic blood pressures did not show much difference either pre or post intubation and we concluded that both the drugs didn't have much effect on diastolic blood pressures. Mean arterial pressure were similar in both groups at all times except 1 min post intubation where it was lower in Labetalol group (P Value < 0.05). Rate pressure product (Heart Rate X Systolic Blood Pressure) shows decreased values in Labetalol group as compared to Esmolol group and was statistically significant (P Value < 0.05) at all times except preinduction.

**Table 1: Demographic profile, duration of surgery & intubation time**

Parameters	Esmolol(E) Mean±SD	Labetalol(L) Mean±SD	P Value
Age	33±5.40	33.4±5.32	0.7736
Weight(KG)	54.26±3.46	54.4±3.60	0.8844
Height(CM)	159.83±3.16	159.63±2.89	0.7993
Sex(M/F)	15/15	15/15	1
Duration of Surgery(MIN)	95.66±9.25	96.16±8.57	0.8290
Intubation Time(SEC)	11.76±1.95	12±1.87	0.6393

**Table 2: Pulse Rate**

Pulse rate	Group E (min)	Group L (min)	P value
Preinduction	85.76±8.33	85.24±14.26	0.876
At intubation	108.64±11.1	97.4±9.01	<0.001
<b>Post Intubation</b>			
1 min	109.64±8.57	98.16±10.6	<0.001
3 min	97.44±9.17	90.56±11.03	0.020
5 min	93.68±12.25	85.28±11.35	0.015
10 min	90.16±11.23	76.16±7.76	<0.001

**Table 3: Systolic Blood Pressure**

	Group E (mm Hg)	Group L (mm Hg)	P value
Preinduction	121.04±9.14	126.08±10.57	0.078
At Intubation	154.24±17.35	140.72±16.99	0.008
<b>Post Intubation</b>			
1 min	158.72±16.77	139.36±12.56	<0.001
3 min	137.44±16.44	125.04±11.33	0.003
5 min	127.36±14.62	118.32±10.12	0.014
10 min	121.68±9.12	113.68±11.3	0.008

**Table 4: Diastolic Blood Pressure**

	Group E (mm Hg)	Group L (mm Hg)	P value E and L
Pre induction	79.12±6.9	81.28±5.82	0.238
At intubation	98.8±6.95	100.64±13.67	0.551
<b>Post intubation</b>			
1 min	94.96±6.48	97.52±9.92	0.286
3 min	87.36±6.23	89.76±6.61	0.193
5 min	82.40±6.29	82.80±9.11	0.857
10 min	78.96±6.80	79.04±7.53	0.969

**Table 5: Mean Arterial Pressure**

Mean Arterial Presssure	Group E (mm Hg)	Group L (mm Hg)	P value E and L
Preinduction	93.09±7.03	96.21±5.80	0.094
At intubation	117.28±8.53	114.00±13.33	0.305
<b>Post intubation</b>			
1 min	116.21±6.90	111.46±9.01	0.042
3 min	104.05±8.09*	101.52±6.71	0.234
5 min	97.38±8.08	94.64±8.36	0.244
10 min	93.2±6.74	90.58±8.12	0.222

**Table 6: Rate Pressure Product**

RPP	Group E (mm Hg /min)	Group L (mm Hg /min)	P value
Preinduction	10420±1562	10726±1889	0.535
At intubation	16894±3203	13719±2136	<0.001
<b>Post intubation</b>			
1 min	17471±2746	13647±1769	<0.001
3 min	13438±2325	11336±1846	0.007
5 min	11995±2468	10143±1938	0.001
10 min	11017±1957	8680±1401	<0.001

## Discussion

Laryngoscopy and intubation may be associated with various dysrhythmias which are generally transient and well tolerated by healthy patients,<sup>1</sup> but it may be fatal for a patient with known cardiac disease. So most clinicians use adjuncts to attenuate the sympathetic response in high risk patients. Beta blockers have been compared with Fentanyl,<sup>3,4</sup> Nitroprusside,<sup>5</sup> Nitroglycerine,<sup>6</sup> calcium channel blockers,<sup>7</sup> etc. However, studies comparing Esmolol<sup>8-11</sup> (cardioselective beta blocker) and Labetalol<sup>12</sup> (nonselective adrenergic blocker) are few. Esmolol hydrochloride is an ultra-short acting, beta-one selective adrenergic receptor blocker with a distribution half-life of 2 minutes and an elimination half-life of 9 minutes. It is suitable for use during a short-lived stress such as tracheal intubation. Labetalol is an adrenergic receptor blocking agent with mild alpha and predominant beta-adrenergic receptor blocking actions (alpha: beta blockade ratio of 1:7 for intravenous and 1:3 for oral administration). Equipotent dose of esmolol is approximately 10 times of labetalol dose.

The onset of action of intravenous Labetalol is 5 minutes. With this background we conducted this prospective, randomized, comparative clinical study, using Esmolol (0.5 mg/kg) and Labetalol (0.25mg/kg) given 2minutes and 5minutes prior to intubation respectively.

We studied the hemodynamic response to laryngoscopy and intubation for a period of 10 minutes as this is the average period for which hemodynamic changes are believed to last.

Labetalol had a significantly ( $P<0.05$ ) better effect than Esmolol in controlling pulse rate at all points during the study. Esmolol showed no significant effect on pulse rate. When instrumentation stimulus is present Labetalol maintains the pulse rates within normal ranges. After 10 minutes post intubation when stimulus effect weans off the drug's effect takes over and pulse rates go below baseline values.

In preventing the increases in systolic Blood Pressure Esmolol was completely ineffective. Labetalol prevented the increase in SBP significantly throughout the study period ( $P<0.05$ ). Ramanathan *et al*<sup>13</sup> used 20 mg Labetalol to prevent rise in SBP successfully. As per Inada *et al* [14], 10 mg (0.14 mg/kg) Labetalol was ineffective in attenuating the rise in systolic pressure. This difference could be the result of lower doses used and timing of drug administration

Maharaj *et al*.<sup>15</sup> failed to blunt the blood pressure response with 0.25 and 0.5 mg/kg labetalol. However, they did not mention the timing of giving the drug. Esmolol even in doses exceeding >1mg/kg have been found to be ineffective in controlling systolic pressure rise.

Derbyshire DR *et al* stated that tracheal intubation is accompanied by sympathetic and sympathoadrenal

activity so suppression of pressor response requires both alpha and beta adrenergic blockade.<sup>16</sup> In our study we got the same results as labetalol causing both alpha and beta lockade scored over beta-1 selective esmolol in preventing pressor response.

Diastolic blood pressure was not attenuated ( $P>0.05$ ) in any of the study groups. No significant difference was observed in intergroup comparison of Esmolol and Labetalol, ( $P>0.05$ ). Between Esmolol and Labetalol there was no significant difference in values except at 1 minute postintubation (Labetalol having lower MAPs,  $P<0.04$ ). This observation was again an isolated finding and no significant difference ( $P>0.05$ ) was found at any other point during the study period. MAP increase was attenuated by Labetalol but not Esmolol.

RPP is an index of myocardial oxygen consumption.<sup>17</sup> It is the product of SBP and HR. Values in excess of 15,000 are considered critical. Increase in RPP due to increase in HR is potentially more deleterious than that due to increase in blood pressure.<sup>8,18</sup> In Esmolol-treated patients Rate Pressure Product(RPP) was not significantly different from the control group. Compared to Esmolol groups, the Labetalol group had significantly lower values of RPP. Labetalol could not prevent the increase in RPP completely, but values never crossed the critical limit of 15000 mmHg/min. The values returned to baseline at 3 min post intubation as compared to other group where baseline values were achieved at 10min. Therefore, Labetalol (0.25mg/kg) decreases the magnitude and duration of hemodynamic response to laryngoscopy as evident from changes of RPP. Leslie *et al*.<sup>19</sup> used Labetalol in doses of 0.25, 0.5, 0.75 and 1.0 mg/kg and found all doses effective in controlling the rise in RPP at laryngoscopy.

Labetalol caused bradycardia intraoperatively in seven patients (28 %) (Pulse rate <50 beats per minute) after the study period of 10 min. Atropine 0.6 mg was given and all the patients responded well. There were no recurrent episodes of bradycardia. No other side effects were observed. There were no abnormal ECG changes between the duration of induction and intubation.

## Conclusion

From our study we concluded that in lower doses, Labetalol (0.25 mg/kg) is more effective than Esmolol (0.5 mg/kg) in attenuating the sympathomimetic response to laryngoscopy and intubation. Bradycardia is a potential side effect of Labetalol which is easily treatable.

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