TO EVALUATE EFFECT OF IV ESMOLOL (1MG/KG) COMPARED TO I.V. LABETALOL (0.5MG/KG) IN ATTENUATING PRESSOR RESPONSE DURING LARYNGOSCOPY & INTUBATION IN GENERAL ANESTHESIA

B. Sowbhagya Lakshmi¹, M. Santhi Sree², P. Krishna Prasad³, Vasudeva Rao⁴

ABSTRACT: BACKGROUND: Laryngoscopy and endotracheal intubation is invariable in G.A. and is associated with increased sympathomimetic response. The present study compared the efficacy of esmolol and labetalol in low doses for attenuation of pressor response.

MATERIALS & METHODS: This is a Prospective, randomized, placebo controlled study in which 75 ASA Grade I and II patients aged 18-45 yrs. undergoing elective surgical procedures, requiring G.A. and orotracheal intubation were taken up for the study. Patients were allocated to any of the three groups of (25 each). Group C (Control) received 10ml of 0.9% saline IV, Group E (Esmolol) were given 1mg/kg of drug diluted with 0.9% saline 10ml IV, Group L (Labetalol) were given 0.5mg/kg of the drug diluted with 0.9% saline 10ml IV. All the patients were subjected to the same anesthesia technique. HR, SBP, DBP were recorded prior to intubation, then 1 minute, 3 min, 5 min and upto 10min post intubation.

RESULTS: Compared to placebo, esmolol and labetalol significantly attenuated HR, SBP, DBP during laryngoscopy and intubation. CONCLUSION: In lower doses, labetalol is a better agent than esmolol in attenuating the sympathomimetic response to laryngoscopy and intubation.

KEYWORDS: esmolol, labetalol, pressor response, general anesthesia.

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. Laryngoscopy and endotracheal intubation are mandatory for most patients undergoing general anesthesia, which is invariably associated with certain cardiovascular changes such as tachycardia or bradycardia, rise in blood pressure and a wide variety of cardiac arrhythmias. These effects are deleterious in susceptible individuals culminating in perioperative myocardial ischemia, acute heart failure and cerebrovascular accidents.

The response following laryngoscopy and intubation peaks at 1-2 minutes and returns to normal within 5-10 minutes. Various systemic as well as topical agents were used to reduce these untoward hemodynamic responses due to laryngoscopy and intubation. The pharmacological methods are aimed at efferent, afferent or both limbs of response eg. Volatile inhalational agents,¹ lignocaine,² opioids,³ sodium nitroprusside,⁴ nitroglycerine⁵ Calcium channel blockers,⁶ and adrenergic blockers.⁷ Most of the studies used esmolol⁸⁻¹² (Cardio selective beta blocker) as bolus and in infusion and found it to be effective.

Other beta blockers like metoprolol¹³, ¹⁴ and labetalol¹⁵, ¹⁶ have been useful in not only attenuating the response of laryngoscopy and intubation but also in preventing perioperative cardiovascular events. Intravenous esmolol due to its ultra-short action seem to be ideal to control intense but brief sympathetic stimulation following endotracheal intubation.
Esmolol hydrochloride is a beta 1-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes). It has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes. Esmolol hydrochloride is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells.

Labetalol, a combined $\alpha_1$ and non-selective $\beta$-adrenergic blocking drug has shown a better safety profile and hemodynamic stability. Onset time after IV administration is 5 minutes; peak effect is seen at 5-15 minutes, with a half-life of 4-6 hrs.

It reduces systemic vascular resistance & reflex tachycardia and is not associated with rebound hypertension. It has low placental transfer due to high degree of ionization at physiological pH. As there are no studies comparing Esmolol and labetalol in attenuating pressor response, we undertook the study to compare them.

**AIM OF THE STUDY:** The hemodynamic response during laryngoscopy and intubation should be abolished to balance the myocardial oxygen supply and demand for the safe conduct of anesthesia. This study was done to compare intravenous Esmolol and labetalol in attenuating the hemodynamic stress responses to laryngoscopy and endotracheal intubation.

**MATERIALS & METHODS:** After obtaining institutional ethical committee approval and informed consent from patients, this prospective, randomized, controlled study was conducted in 75 ASA I & II patients aged 18-45 yrs., undergoing surgeries under GA. The study was conducted during March 2013 to January 2014. The patients were randomly (Computer generated randomization schedule) allocated into one of the three groups, of 25 each.

Patients were allocated to any of the three groups:

- **Group C** (control) group were given 10ml 0.9% saline i.v.
- **Group E** (Esmolol) group were given 1.0 mg/kg diluted with 0.9% saline to 10ml i.v.
- **Group L** (Labetalol) group were given 0.5 mg/kg diluted with 0.9% saline to 10ml i.v.

**Inclusion Criteria:**

- ASA I & II.
- Age 18-45 yrs.
- All cases requiring GA.

**Exclusion Criteria:**

- Patients with known difficult airways.
- Patients with bronchial asthma.
- Patients on beta blockers.
- Patients with full stomach.
- Patients posted for Emergency surgery.
- Patients with Hypertension, Diabetes, Ischemic heart disease.
All the patients were admitted and they underwent relevant investigations. Preoperatively informed, written consent was obtained from the patients. Preoperative visit was done to allay anxiety and good rapport was established with the patient. All the patients were given preoperative night sedation with tablet Diazepam 10 mg and antacid prophylaxis with tablet Ranitidine 150 mg orally.

The patients were then shifted into the operating room, IV access was secured with 18G cannula and connected to monitors; ECG, NIBP and pulse oximeter, and baseline values were recorded. Induction of anesthesia was standardized for all the patients. All the patients were premedicated with Inj. Glycopyrrolate 4µg/kg body weight, intravenously, and basal pulse rate and blood pressure were recorded. Pre-oxygenation was done with 100% oxygen for 3 minutes. The study drug was diluted to 10ml and given as bolus over 15-20 seconds two minutes before intubation for esmolol & 5 min before for labetalol.

One minute later anesthesia was induced with 2.5% inj. Thiopentone sodium 5mg/kg IV. and inj. Succinyl choline 1.5mg/ kg IV given. After satisfactory muscle relaxation, the patients were intubated with appropriate size endotracheal tube after doing a proper laryngoscopy within 20 seconds. Conditions with prolongation of laryngoscopy time due to difficult intubation were excluded from the study. Endotracheal tube was secured after confirming bilateral air entry. Anesthesia maintained with N20 & 02 (66.7%: 33.3%) and IPPV was done. The ETC02 was maintained at 35-45 mmHg.

**STATISTICAL ANALYSIS:** Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure are recorded and analyzed. All recorded data were entered using MS Excel software and analysed using SPSS software for determining the statistical significance. Patient’s demographics were compared with analysis of variance (ANOVA). The study data was analysed using statistical methods of mean, standard deviation, paired “t” test (for values within the group at different time stations) and independent samples “t” test (for comparison of intergroup values).

The p-value taken for significance is <0.05.

**RESULTS:** Analysis of patient’s results revealed no differences in the demographic characteristics of the three groups (Tab-I). The pre-induction values of pulse rate (PR) were comparable between groups with no significant difference. (Tab -II) There was no statistically significant difference in PR throughout study time between esmolol and control group (p>0.005). At intubation and 1 min post intubation PR was significantly lower in labetalol group compared to the control group (p<0.001 and p=0.0106 respectively at 3 and 5 min post-intubation).

There was no significant difference in PR (p=0.17 and p=0.39 respectively) between labetalol and control groups. At 10th minute PR was significantly lower in the labetalol group than the control group (p<0.001). The PR were significantly less in the labetalol group throughout the study time compared to esmolol group (<0.001 at intubation and 1st minute post-intubation, p=0.0146 at 3rd minute, p=0.02 at 5th and p<0.001 at 10th minute post-intubation).

The pre-induction values of SBP were comparable between groups with no significant differences (Tab-III). SBP increased in both esmolol and control groups at all times. However, no significant difference was present between the groups (p > 0.05). Compared with the control group values (Tab-III) SBP was significantly lower at all time in the labetalol group (p<0.001 and p=0.0168...
at 10th minute post intubation). SBP was significantly less in patients receiving labetalol compared to those who received esmolol (p<0.01 at intubation and 1, 3 and 10 min post intubation and p = 0.0071 at 5 min post intubation).

The pre-induction values of DBP were comparable between groups with no significant differences (Tab-IV). Table IV shows that DBP at 1 minute post-intubation in the esmolol group was significantly less than that in the control group (p=0.009). At all other times it was comparable between the groups (p>0.05), DBP in the labetalol group was comparable with the control group with no significant differences. Diastolic pressures were not significantly different between labetalol and esmolol groups (p>0.05).

The pre-induction values of MAP were comparable between groups with no significant differences (Tab-V). Map was significantly less at the time of intubation in the esmolol group (p<0.05) compared with the control group. All other post-intubation values were comparable between the two groups and not statistically significant (p>0.1) compared with controls (Tab-V), it was significantly less in the labetalol group at all times except at 10th minute post-intubation (p=0.012 at intubation, p<0.01 at 1st and 3rd minute postintubation).

There was no statistically significant difference between values of labetalol and esmolol groups (p>0.15), except at 1min post-intubation when it was significantly less in the labetalol group (p=0.0008).

**DISCUSSION:** Many adjuncts are used to attenuate the sympathetic response associated with laryngoscopy and intubation, particularly in high risk patients. Beta blockers have been compared with fentanyl, nitroprusside, nitro glycerine, Calcium channel blockers etc., however studies comparing esmolol (Cardioselective beta blocker) and labetalol (Non selective adrenergic blocker) are lacking.

Esmolol hydrochloride is an ultra-short acting, beta-one selective adrenergic receptor blocker with a distribution half-life of 2 min and an elimination life-life of 9 min. Esmolol appears quite suitable for use during a short-lived stress such as tracheal intubation or ECT. Labetalol is an adrenergic receptor blocking agent with mild alpha1- and predominant beta-adrenergic receptor blocking actions (alpha: beta blockade ratio of 1:7 for IV and 1:3 for PO administration).

The onset of action of i.v. labetalol is 5 min. We studied the hemodynamic response to laryngoscopy and intubation for a period of 10 mins, as this is the average period of for which hemodynamic changes are believed to last. There was no significant effect of esmolol on pulse rate when compared to control group. Labetalol had a significantly (p<0.05) better effect than esmolol in controlling pulse rate at all points during the study. It seems that when instrumentation stimulus is present labetalol maintains the pulse rate within normal ranges.

When the effect of stimulus weans off, as occurs at 10 min postintubation, the drug’s effect takes over and pulse rates go below baseline values. Labetalol prevented the increase in SBP significantly throughout the study period as compared to control and esmolol groups (p<0.05). The rise in DBP was not attenuated in any of the study groups and inter group study also none of them is superior. Esmolol group has significantly less MAP at intubation compared with control group. When labetalol was compared with control group the MAP was significantly less at all points except at 10th mins post intubation.
When intergroup was compared, MAP rise was attenuated by labetalol, but not esmolol. The only side effect observed was that of labetalol in form of bradycardia, intraoperatively. Seven patients (28%) developed bradycardia (pulse rate <50 beats per minute) after the study period of 10 min and atropine in 0.2 mg increments (max. 0.01 mg/kg) was given. All the patients responded to atropine treatment. There were no recurrent episodes of bradycardia.

CONCLUSION: Labetalol in doses of (0.5mg/kg) is better agent than esmolol (1.0mg/kg) in attenuating the sympathomimetic response to laryngoscopy and intubation.

REFERENCES:
1. Bedford RE, Feinstein B. Hospital admission blood pressure predictor for hypertension following endotracheal intubation. Anesth Analg 1980; 59: 367-70.
2. Stoelting RK. Blood pressure and heart rate charges during short duration laryngoscopy for tracheal intubation: influence of viscous or intravenous indocaine. Anesth Analg 1978; 57; 197-9.
3. Martin DE. Rosenberg H, Aukburg SJ, Barkowski RR, Edwards MW Jr, Greenhow DE, et al. Low dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 1982; 61: 680-4.
4. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 1979: 58: 116-9.
5. Kamra S, Wig J, Sapru RP. Topical nitroglycerine: A safeguard against pressor response to tracheal intubation. Anaesthesia 1986; 41: 1087-91.
6. Mikawa K, Nishina K, Maekawa M, Obera H. Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation. Br J Anaesth 1996; 76: 221-6.
7. Nami K, Takahi K, Tanaka K, Shuzo O. A comparison of landiolol and esmolol for attenuation of cardiovascular response and plasma rennin activity against tracheal intubation with laryngoscopy. Anesthesiology 2005: 103: 433.
8. Sharma S, Mitra S, Grover VK, Kalra R. Esmolol blunts the haemodynamic responses to tracheal intubation in treated hypertensive patients. Can J Anaesth 1996: 43:778-82.
9. Ebert TJ, Bernstein JS, Stews DF, Roering D, Kampine JP. Attenuation of hemodynamic responses to rapid sequences induction and intubation in healthy patients with a single bolus of esmolol. J Clin Anesth 1990; 2: 243-52.
10. Rathora A, Gupta HK, Tanwat GL. Attenuation of the pressure response to laryngoscopy and endotracheal intubation with different doses of esmolol. Indian J Anaesth 2002: 46: 449-52.
11. Oda Y, Nishikawa K, Hase I, Asada A. The short acting – 1 adrenoceptor anagntagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. Anesth Analg 2005:100:733-7.
12. Oxorin D, Know JW, Hill J. Bolus doses of esmolol for the preventing of perioperative hypertension and tachycardia. Can J Anaesth 1990; 37: 206-09.
13. Zargar JA, Nagash IA, Gurcoo SA, Mehraj-ud-din. Effect of Metoprolol and esmolol on rate pressure product and ECG changes during laryngoscopy and tracheal intubation in controlled hypertensive patients. Indian J Anaesth 2002:46:365-8.
14. Magnusson J, Warner D, Cartsson C Norden, N. Pettersson, Kl. Metoprolol, fentanyl and stress response to micro laryngoscopy. Effect on arterial pressure, heart rate and plasma concentration of catecholamines. ACTH and cortisol. Br J Anaesth 1983: 55: 405-14.
15. Kim HY. Chung CW. Lee HY, Yim CH. The Effect of labetalol on the hemodynamic response to endotracheal intubation. Korean J Anesthsiol 1994: 27: 1611-9.
16. Chung KS, Sinatra Rs, Chung JH. The effect of an intermediate dose of labetalol on heart rate and blood pressure response to laryngoscopy and intubation. J Clin Anesth 1992; 4:11-5.
17. Inada E, Cullen DJ, Nemeskal R, Teplick R. Effect of labetalol on the hemodynamic response to intubation: a controlled randomized double – blind study. J Clin Anesth 1989: 1:207-13.
18. Ramanathan J, Sibai BM, Madie WC, Chauhan D, Ruiz AG. The use of labetalol for attenuation of hypertensive response to endotracheal intubation in preecampsia. Am J Obstet Gynecol 1988: 159: 550-4.
19. Forbes AM, Dally FC. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 1970: 42: 618-24.
20. Maharaj RJ, Thompson M, Brock JG, Williamson R, Downing JW. Treatment of hypertension following endotracheal intubation- A study comparing the efficacy of labetalol, practolol and placebo. S Afr Med J 1983: 63: 691-4.

| GROUP E | GROUP L | GROUP C | P-VALUE C&E | P-VALUE C&L |
|---------|---------|---------|-------------|-------------|
| Age (years) | 35.9±8.6 | 35.1± 8.7 | 34.9±8.4 | > 0.05 (0.62) | >0.05 (0.93) |
| Sex (M: F) | 2:1 | 1:1 | 1.5:1 |
| Weight (kgs) | 56.4 | 57.8 | 58.3 |

**TABLE I: SHOWING DEMOGRAPHIC DATA**

| | GROUP C (/min) | GROUP E (/min) | GROUP L (/min) | P value C & E | P value C & L | P value E & L |
|---|---|---|---|---|---|---|
| Pre induction | 83.11±10.16 | 86.11±8.14 | 86.35 ±13.10 | 0.2549 | 0.3334 | 0.9383 |
| At intubation | 115.83±15.33 | 109.18 ±10.20 | 98.39 ± 8.98 | 0.0772 | 0.0001 | 0.0002 |
| Post intubation | | | | | | |
| 1 min | 108.32±14.15 | 110.23±8.63 | 99.01±10.3 | 0.5672 | 0.0106 | 0.0001 |
| 3 min | 95.16±9.88 | 98.38 ±9.20 | 91.10±11.03 | 0.2389 | 0.1768 | 0.0146 |
| 5min | 88.74±9.12 | 94.19±12.26 | 86.22±11.35 | 0.0809 | 0.3911 | 0.0211 |
| 10min | 86.18±7.02 | 90.13±11.18 | 77.14±7.76 | 0.1412 | <0.0001 | 0.0001 |

**TABLE II: SHOWING PULSE RATE**
|                   | Group C (mmhg) | Group E (mmhg) | Group L (mmhg) | P value C & E | P Value C & L | P value E & L |
|-------------------|----------------|----------------|----------------|--------------|--------------|--------------|
| Pre induction     | 123.8±9.88     | 122.00±9.14    | 126.08±10.57   | 0.5069       | 0.4346       | 0.1508       |
| At intubation     | 164.3±14.3     | 153.12±17.35   | 140.72±16.99   | 0.0164       | 0.0001       | 0.0139       |
| Post intubation   |                |                |                |              |              |              |
| 1 min             | 157.00±14.3    | 157.70±16.77   | 139.36±12.56   | 0.8745       | 0.0001       | 0.0001       |
| 3 min             | 141.10±12.37   | 136.33±16.44   | 124.00±11.33   | 0.2521       | 0.0001       | 0.0033       |
| 5 min             | 126.12±10.85   | 126.33±14.62   | 116.32±10.12   | 0.9542       | 0.0018       | 0.0071       |
| 10 min            | 120.24±1       | 122.64±9       | 112.60±1       | 0.3923       | 0.0168       | 0.0012       |

**TABLE III: SHOWING SYSTOLIC BLOOD PRESSURE**

|                   | Group C (mmhg) | Group E (mmhg) | Group L (mmhg) | P value C & E | P value C & L | P value E & L |
|-------------------|----------------|----------------|----------------|--------------|--------------|--------------|
| Pre induction     | 80.44±5.34     | 79.10±7.0      | 82.30±5.82     | 0.4504       | 0.2448       | 0.0852       |
| At intubation     | 101.02±6.86    | 99.10±6.95     | 100.30±13.67   | 0.3305       | 0.8149       | 0.6973       |
| Post intubation   |                |                |                |              |              |              |
| 1 min             | 100.10±6.53    | 95.16±6.48     | 97.50±9.92     | 0.0099       | 0.2791       | 0.3284       |
| 3 min             | 92.00±7.00     | 88.30±6.23     | 90.14±6.61     | 0.0541       | 0.3389       | 0.3162       |
| 5 min             | 86.10±7.09     | 83.22±6.29     | 82.66±9.11     | 0.1352       | 0.1428       | 0.8014       |

**TABLE IV: SHOWING DIASTOLIC BLOOD PRESSURE**

|                   | Group C (mmhg) | Group E (mmhg) | Group L (mmhg) | P value C & E | P value C & L | P value E & L |
|-------------------|----------------|----------------|----------------|--------------|--------------|--------------|
| Pre induction     | 94.23±5.50     | 93.40±7.03     | 96.10±5.80     | 0.6441       | 0.2479       | 0.0977       |
| At intubation     | 123.14±8.24    | 118.28±8.53    | 113.11±8.33    | 0.0460       | 0.0001       | 0.0351       |
| Post intubation   |                |                |                |              |              |              |
| 1 min             | 119.10±7.74    | 117.20±6.90    | 110.27±6.71    | 0.3641       | 0.0001       | 0.0008       |
| 3 min             | 108.34±7.66    | 105.10±8.09    | 100.44±6.71    | 0.1524       | 0.0003       | 0.0314       |
| 5 min             | 100.01±7.49    | 98.20±8.08     | 94.56±8.36     | 0.4155       | 0.0190       | 0.1241       |
| 10 min            | 94.50±5        | 93.3±6.7       | 88.00±8        | 0.5059       | 0.0022       | 0.0155       |

**TABLE V: SHOWING MEAN BLOOD PRESSURE**
**AUTHORS:**
1. B. Sowbhagya Lakshmi
2. M. Santhi Sree
3. P. Krishna Prasad
4. Vasudeva Rao

**PARTICULARS OF CONTRIBUTORS:**
1. Professor and HOD, Department of Anaesthesia, Rangaraya Medical College, Government General Hospital, Kakinada.
2. Assistant Professor, Department of Anaesthesia, Rangaraya Medical College, Government General Hospital, Kakinada.
3. Associate Professor, Department of Anaesthesia, Rangaraya Medical College, Government General Hospital, Kakinada.
4. Post Graduate, Department of Anaesthesia, Rangaraya Medical College, Government General Hospital, Kakinada.

**NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. M. Santhi Sree,
D. No. 13-2-2, Sai Krishna Towers,
D1 Apartment, Latchiraju Street,
Kakinada-533002, E. G. District, A. P.
Email: santhisreemulam@gmail.com

Date of Submission: 01/08/2014.
Date of Peer Review: 02/08/2014.
Date of Acceptance: 07/08/2014.
Date of Publishing: 14/08/2014.