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Comparison the Effects of Intravenous Esmolol Hydrochloride (0.5 Mg/Kg) and Intravenous Labetolol Hydrochloride (0.25mg/Kg) In Attenuation of Cardiovascular Response to Direct Laryngoscopy and Endotracheal Intubation

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Original Research Article

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Abstract: Laryngoscopy and endotracheal intubation usually induces sympathomimetic responses which may produce life threatening arrhythmias, left ventricular failure or rupture of cerebral aneurysm in susceptible patients. Esmolol and Labetalol attenuate these responses but are associated with side effects like bradycardia, hypotension etc. We have done this prospective clinical trial to assess the efficacy of intravenous esmolol and labetalol for attenuation of sympathomimetic responses to endotracheal intubation. This is a prospective, randomized and placebo controlled study. 75 ASA Grade I and II patients of aged 18-60 yrs posted for elective surgical procedures, requiring endotracheal intubation were included in the study. Patients were allocated to three groups of 25 each. Group C (Control) received 10ml of 0.9% saline IV, Group E were given 1mg/kg of esmolol diluted with 10 ml of 0.9% saline IV, Group L were given 0.5mg/kg of labetalol diluted with 10 ml 0f 0.9% saline IV. All the patients were administered same anesthesia. HR, SBP, DBP and MAP were recorded prior to intubation, then 1 minute, 3 min, 5 min and up to 10min post intubation. Compared to placebo, esmolol and labetalol significantly attenuated HR, SBP, DBP and MAP during laryngoscopy and intubation. Labetalol was a better agent than esmolol in attenuating the sympathomimetic response to laryngoscopy and intubation.

Keywords: Esmolol, labetalol, pressor response, general anesthesia.

INTRODUCTION

The hemodynamic changes resulting from airway instrumentation are due to sympathoadrenal response caused by epipharyngeal and parapharyngeal stimulations [1].

There is increase in heart rate, blood pressure, intraocular and intracranial pressure. It may produce serious challenges in conditions like cardiovascular disease, hypertension, coronary artery disease, aneurysms or those with decreased intracranial compliance like head injury with extra and subdural hematoma formation, intracranial space occupying lesion etc[2]. A sudden rise in blood pressure may cause left ventricular failure, myocardial ischemia and cerebral haemorrhage in vulnerable patients.

Various attempts have been made to suppress this pressure response. The drugs used are volatile inhalational agents, lignocaine, opoids, vasodilators (sodium nitropruside, nitroglycerine, calcium channel blockers and alpha (α) and beta (β) adrenergic blockers etc[3,4].

But no ideal drug has gained popularity. Keeping this in mind, an attempt is made to observe the effect of esmolol hydrochloride (selective β-1 blocker) with labetolol hydrochloride (antagonist at both α and β receptor) on hemodynsmic response to laryngoscopy and endotracheal intubation.

Our primary aim was to observe and compare compare the efficacy of IV labetolol hydrochloride (0.25mg/kg) and IV esmolol hydrochloride (0.5 mg/kg)

in attenuation of hemodynamic response to laryngoscopy and endotracheal intubation. Secondary aim was to observe the occurrence of any drug related adverse effects.

MATERIALS AND METHODS

The proposed study is a hospital based study conducted in VIMSAR, Burla, and Odisha during the period 2015-2017, after approval of institutional ethical committee.

Seventy five patients aged 18 - 60 yrs of ASA I/II, scheduled for various elective surgical procedures under general anesthesia were included in study. Emergency surgical interventions, anticipated difficult intubation and ASA physical status III and IV were excluded from study.The study population were randomly divided into 3 groups of 25 patients each. All routine investigations like haemogram, examination of urine and stool, blood urea, serum creatinine, blood sugar, cardiological evaluation, ECG, X-ray chest etc were done. All patients were advised to remain nil per orally for 8 hrs. On the day of operation, Intravenous line secured with a 18G cannula and Ringer's lactate solution started at 75ml/hr. Patients were premediated intravenously 10 min prior to intubation with inj. ondansetron 0.1 mg/kg), inj. Glycopyronium Bromide(0.2mgIV), inj. Midazolam Hydrochloride(0.05mg/kg), inj. Butorphanol Tartarate (0.03mg/kg IV). Continuous monitoring of SPO2, HR, NIBP, and ECG was done. Preoxygenation was done with 100% 02 by a face mask for 3 min. In the group C 10 ml of 0.9% saline was given 2 mins prior to intubation. In the group E, 0.5 mg/kg of esmolol (diluted with 0.9% saline to 10 ml) was given 2 mins prior to intubation and in the group L, 0.25 mg/kg of labetalol (diluted with 0.9% saline to 10 ml) was given 5 min prior to intubation. Induction and intubation was done with inj Thiopentone 5 mg/kg and inj Succinyl choline 2mg/kg IV.

Anesthesia was maintained by N2O (60%) and O2 (40%). Bolus IV injection of Vecuronium Bromide 0.1mg/kg followed by intermittent doses of (0.02mg/kg). At the end of surgical procedure, the residual effect of muscle relaxant (neuromuscular blockade) was reversed with inj. Neostigmine methyl (0.05mg/kg) and inj. Glycopyrronium bromide (0.01mg/ kg)

Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Mean arterial pressure (MAP) were recorded in all the patients. The above cardiovascular parameters were noted before administration of study drug, at the time of administration of study drug, at the time of laryngoscopy & intubation and after intubation at 1 min, 3 min, 5 min,10 min and 15 min. Patient demographics were compared with analysis of variance (ANOVA). Sample size was calculated by power analysis, type I error of 5% (α=0.05) and power at 80.37 (α=0.19). 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).

RESULTS

The age distribution of all the three groups were comparable (p>0.05). Mean age in control group (group – C) was 31±2.8, Esmolol group (group-E) was 31.24±7.3 & Labetalol group (group- L) was 30.56±7.1.The patients in the three groups were comparable (p>0.05) with respect to sex. The weight distribution of all the three groups were comparable (p>0.05). The mean weight in group– C was 58.84±4.9 kg, group-E was 59.56±3.6 kg & group- L was 60.2±4.9 kg.

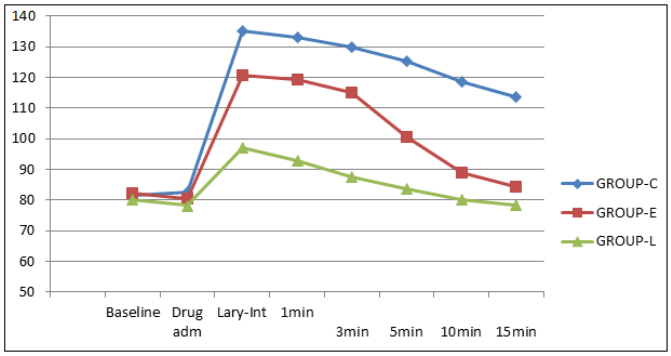

Fig-1: Mean Pulse Rate (beats/min) at different time intervals in the three groups

The pulse rate in control group (C), esmolol group (E) & labetalol group (L) at baseline & after study drug administration were comparable, with mean value in group C being 81.72 & 82.76, in group-E being 82.28 & 80.56, in group-L 80.08 & 78.2beats per minute. At intubation in group-C, increase in mean pulse rate from baseline mean to 133.2±4.72 per min & gradual decrease subsequently with 1 min, 3 min ,5 min ,10 min & 15 post intubation respective values of 129.72±4.96, 125.36±5.32 ,118.6±5.01, 113.52±4.86 beats per min. (Fig1) In esmolol group, mean pulse rate raised to 120.84±8.52(beats/min) at laryngoscopy & intubation and 1min ,3 min ,5min ,10 min,15 min post intubation the mean pulse rate were 119.36±8.45,

114.96±7.78, 100.64±6.71, 89±5.69 & 84.36± 4.97(beats/min) respectively. Whereas in labetalol group lower increase of mean pulse rate at laryngoscopy to around 97±10.92 (beats/min) & at 1 min, 3min, 5 min, 10 min, 15 min post intubation mean pulse rate were 92.92±10.04, 87.6±7.48, 83.52 ±6.22, 80±5.10, 78.44±4.17 (beats/min) respectively.

Table-1: (Inter group comparison (p value) of pulse rate at various time intervals)

	P value C & E	P value C & L	P value E & L
Baseline	0.823	0.507	0.393
After study drug administration	0.367	0.051	0.345
At Laryngoscopy-Intubation	<0.001	<0.001	<0.001
Postintubation- 1min	<0.001	<0.001	<0.001
3min	<0.001	<0.001	<0.001
5min	<0.001	<0.001	<0.001
10min	<0.001	<0.001	<0.001
15min	<0.001	<0.001	<0.001

Preoperative baseline pulse rate was comparable, between the three groups ,no statistically significant difference was found between the groups ,so also the difference was statistically insignificant after administration of drugs (p > 0.05) .pulse rate was significantly lower in labetalol group (p<0.001) compared to both esmolol & control group at all times(ie at intubation & post intubation) Esmolol also decreased pulse rate significantly at all times (ie at intubation & post intubation) (p<0.001) compared to control group.(table-1)

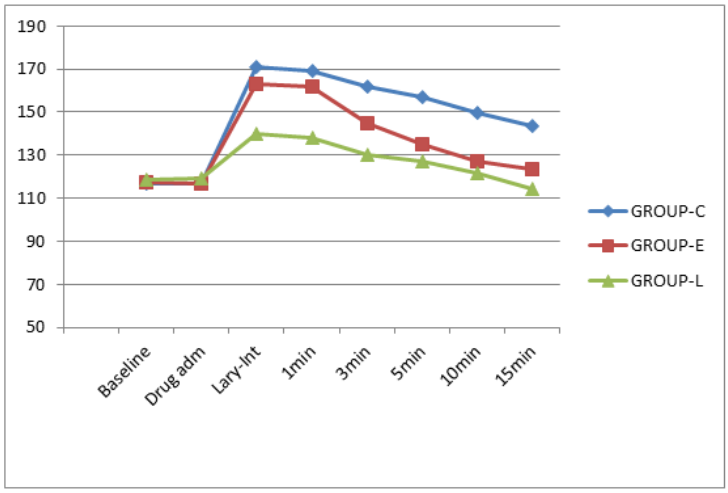

Fig-2: Mean Systolic Blood Pressure at different time intervals in the three groups

Reintubation baseline systolic BP were 116.84±6.71, 117.64±7.15, 118.56±4.7 mmHg in Group-C, E and L respectively. At intubation SBP was raised to 170±5.8 mmHg in control group and to 163.28±6.2 in Esmolol group gradually decreasing over time. Group-L SBP rose to 140.04±6.71 at intubation with subsequent decrease, even decreasing below basline value at 15min to 114.52±5.83mmHg (fig2).

Table-2: (Inter group comparison (p value) of SBP at various time intervals)

	P value C & E	P value C & L	P value E & L
Baseline	0.685	0.299	0.593
After study drug administration	0.967	0.176	0.195
At Laryngoscopy-Intubation	<0.001	<0.001	<0.001
Postintubation- 1min	<0.001	<0.001	<0.001
3min	<0.001	<0.001	<0.001
5min	<0.001	<0.001	0.001
10min	<0.001	<0.001	0.022
15min	<0.001	<0.001	<0.001

The preanaesthetic baseline systolic blood pressure and values after study drug administration were comparable between the three groups with p value >0.05). Compared with the control group values SBP was significantly lower at all time stations (at & post intubation) in the both esmolol & labetalol group (P<0.001). SBPs were significantly less in patients receiving labetalol compared to those who received esmolol (P<0.001 at intubation and 1st, 3rd and 15th minute postintubation, P=0.001 at 5th minute and P=0.022 at 10th minute postintubation). (Table-2)

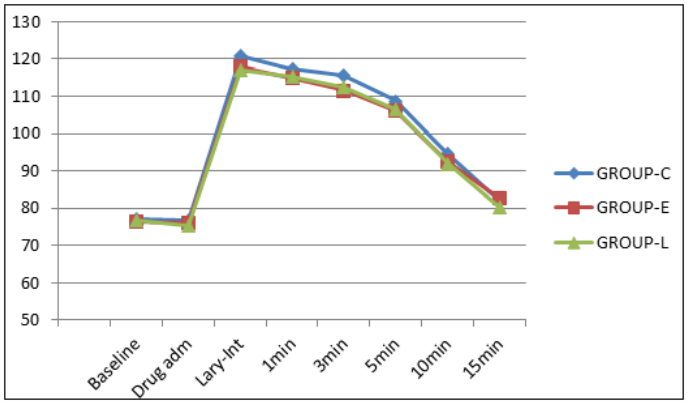

Fig-3: Mean DBP (mmHg) at different time intervals in the three groups

Baseline mean diastolic blood pressure in group-C was 77.04±7.2 & 76.76±.7 mmHg after study drug administration, which increased to 120.72±6.3 at intubation & subsequent gradual decrease, mean DBP being 117.4±6.3, 115.4±6.9, 108.7±6.3, 94.6 ±7.2, 81.8±6.8 mmHg at 1, 3, 5,10, 15 min post intubation respectively. Esmolol & Labetalol group also showed similar trend. Group-E DBP were 76.3±6.6, 76±6.8, 118±6.72, 114.9±7.3, 111.5±7.3, 106.1±7.4, 92.6±9.25, 82.52±7.6 mmHg at Baseline, after study drug administration, at laryngoscopy-Intubation, post intubation- 1min, 3min, 5min, 10min, 15min respectively. Group-L baseline was 76.56±7.69, increased to 117.12±7.65 at intubation and decreased to 80.24±4.36 at 15 min post intubation (fig-3).

Table-3: (Inter group comparison (p value) of DBP at various time intervals

	P value C & E	P value C & L	P value E & L
Baseline	0.714	0.821	0.906
After study drug administration	0.693	0.500	0.785
At Laryngoscopy-Intubation	0.147	0.076	0.667
Postintubation- 1min	0.209	0.260	0.941
3min	0.061	0.163	0.651
5min	0.184	0.396	0.842
10min	0.398	0.265	0.807
15min	0.741	0.330	0.200

Preoperative baseline diastolic pressure & DBP after administration of the study drugs were comparable in all the three groups, their difference was statistically insignificant (Table 6a & 6b).so also the differences of DBP after intubation & all studied times post intubation were statistically insignificant in all the three group(table-3).

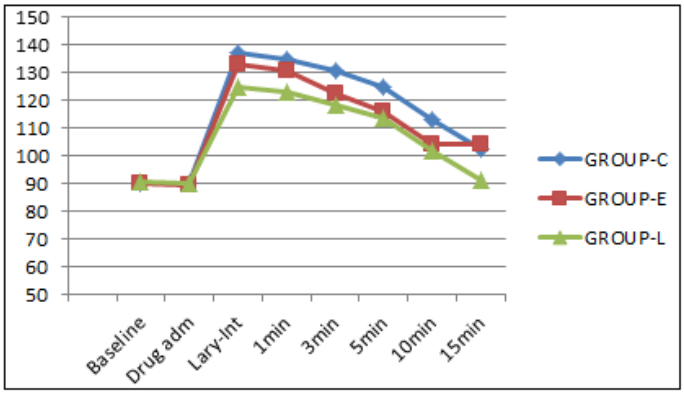

Fig-4: Mean arterial pressures (mmHg) at different time intervals in the three groups

Baseline MAP & MAP after study drug administration were around 90mmHg in all the three groups. MAP increased to 137.44±4.58 mmHg in control & to 133.04±4.71 in Esmolol group, with subsequent decrease but the MAP remained above 100 mmHg in both these groups at 15min. In group-L MAP raised to 124.72±6.81 at laryngoscopy-intubation, with decrease over time, reaching near baseline value at 15min post intubation (91.6±3.58) (fig-4).

Table-4: Inter group comparison (p value) of MAP at various time intervals

	P value C & E	P value C & L	P value E & L
Baseline	0.906	0.906	0.829
After study drug administration	0.715	0.919	0.805
At Laryngoscopy-Intubation	0.001	<0.001	<0.001
Postintubation- 1min	0.005	<0.001	<0.001
3min	<0.001	<0.001	0.031
5min	<0.001	<0.001	0.301
10min	<0.001	<0.001	0.302
15min	<0.001	<0.001	<0.001

Preoperative baseline MAP & mean arterial pressure after administration of the study drugs were comparable in all the three groups, i.e. the difference was statistically insignificant (p>0.05). Difference in mean arterial pressure were statistically significant in both esmolol & labetalol group at all times when compared to control group (p<0.05). When compared to esmolol, labetalol was significantly effective during laryngoscopy & at 1 min (p value <0.001) & 3min(p value 0.031),but was insignificant at 5 min (p value 0.301) & 10 min(p value 0.302).(table-4)

DISCUSSION

Stimulus of the laryngeal and tracheal tissues causes increase in both sympathetic and sympathoadrenal reflex activity [5], which may be a cause of concern in many high risk patients like patients with cardiovascular or cerebrovascular diseases. Different pharmacologic agents like lidocaine [6], vasodilator agents[7], α and β adrenergic blockers[8] and opioids[9] had been administered prior to tracheal intubation in order to prevent haemodynamic responses.

Takeshima *et al*.[10] concluded that laryngoscopy and endotracheal intubation is associated with rise in blood pressure , heart rate and cardiac dysrhythmias. We have used Esmolol hydrochloride (0.5mg/kg) & labetalol hydrochloride (0.25 mg/kg) for attenuating hemodynamic resposes to laryngoscopy endotracheal intubation as very few studies comparing esmolol[11]. (cardioselective beta blocker) and labetalol (nonselective adrenergic blocker) are available Labetalol is an antihypertensive drug that decreases the pressure response of intubation by α1 and β-adrenergic receptor blockade. Presynaptic α2-receptors are spared by labetalol so that the released norepinephrine can continue to inhibit further release of catecholamines via the negative feedback mechanism resulting from the stimulation of α2-receptors.

Labetalol has been used by many researchers like Kim *et al*.[11], Singh *et al*.[12] Inada *et al*.[13] Ramanathan *et al*.[14] and Maharaj *et al*.[15] for the attenuation of hemodynamic response to tracheal intubation in various doses, along with various anesthetic regimens. They have been quite successful in their efforts and have found labetalol effective in attenuating the pressure responses to laryngoscopy and intubation. Adverse effects like hypotension and bradycardia were more frequent in studies with higher doses of labetalol.

Esmolol hydrochloride is an ultra-short acting; selective beta-one adrenergic receptor blocker with a distribution half-life of 2 min and an elimination half-life of 9 min. Esmolol appears quite suitable for use

during a short-lived stress such as tracheal intubation. While doses as high as 2 mg/kg were sufficient but are more than likely to cause adverse effects, 0.5 mg/kg dose is effective enough to attenuate hemodynamic responses and its fast-acting properties allow for a much lower risk of hypotension or bradycardia [12]. In a similar study conducted by Singh *et al*. **[**12] there was no significant effect of Esmolol on pulse rate when compared to the placebo group. Labetalol had a significantly (P<0.05) better effect than Esmolol in controlling pulse rate at all points during their study. Our study is supported by Kim *et al*.[11] who reported that a single dose of Labetalol of dosage 0.25 mg/kg given preoperatively 5 min before intubation decreases HR significantly after intubation up to 10 min. Roelofse *et al.* [16] found that Labetalol of dosage 1 mg/kg given as an IV bolus 1 min before laryngoscopy was not effective in the attenuation of HR. This failure of the study can be explained by the different time of administration of the study drug because Labetalol has peak effect after 5-10min. Our study also corroborates with the findings of Wang *et al*.[17], Rathore *et al*.[18], Suman Shree *et al*.[19].

Ramanathan *et al*.[14] used 20 mg labetalol to prevent rise in SBP successfully. Inad *et al*. [13] found 10 mg (0.14 mg/kg) labetalol ineffective in attenuating the rise in systolic pressure. This difference might be because of the lower dose they used and the timing of giving of labetalol (2 min prior to intubation) because of which the peak effect of drug may not have been attained at intubation. Maharaj *et al*. [15] failed to blunt the blood pressure response with 0.25 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 the rise in systolic pressure. Our study corroborates with the findings of Kumar *et al*. [20] and Ahuja *et al.* [21]. However Rathore *et al*. [18] stated that esmolol successfully suppressed the SBP response even at doses of 50 mg. In the study conducted by Sarvesh P. Singh *et al*. [12]. Esmolol was completely ineffective in preventing the increases in SBP as there was no significant difference between values of Esmolol and placebo groups during the study period (P>0.05). Labetalol prevented the increase in SBP significantly throughout the study period as compared to placebo and Esmolol groups (P<0.05).

The rise in DBP was not attenuated by Esmolol or Labetalol. Our findings corroborate with that of Singh *et al.* [12], Taneja B *et al*. [22] Kinjal J Anand *et al*. [23]. Sharma *et al*. [24] reported that compared to the placebo groups Esmolol at higher doses (200 mg) had a significantly less MAP at intubation. In our study esmolol attenuated MAP at all times (P>0.05) when compared to control, but was less effective when compared to labetalol which corroborates with the observation of Sarvesh P. Singh *et al* [12]. The only side effect observed was that of labetalol in form of bradycardia, intraoperatively. 4 patients (16 %) developed bradycardia (pulse rate <50 beats per minute) after the study period of 15 min and had to be given atropine in 0.2 mg increments (max. 0.01 mg/kg). All the patients responded to atropine treatment. There were no recurrent episodes of bradycardia. No other side effects were observed.

CONCLUSION

The present study compared the efficacy of esmolol and labetalol, in low doses, for attenuation of sympathomimetic response to laryngoscopy and intubation. Compared to control group, both esmolol and labetalol group significantly reduced PR, SBP, and MAP. But the attenuation was more marked in labetalol group. Both labetalol and esmolol are effective in attenuating the increase in heart rate, systolic blood pressure and mean arterial pressure due to layngoscopy and endotracheal intubation but labetalol was superior to esmolol in suppressing the magnitude and duration of haemodynamic response to laryngoscopy and intubation.

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