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COMPARISON OF INTRAVENOUS ESMOLOL WITH INTRAVENOUS LABETALOL FOR SUPRESSION OF HAEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION DURING GENERAL ANAESTHESIA

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ABSTRACT

Objective: The present study compared the efficacy of esmolol and labetalol, for attenuation of sympathomimetic response to laryngoscopy and intubation. **Materials and Methods:** This is a Comparative observational study in which 60 ASA Grade I and II patients aged 18-45 years undergoing elective surgical procedures, requiring G.A. and orotracheal intubation were taken up for the study. Patients were allocated to any of the two groups (30 each). Group E (Esmolol) were given 1.5mg/kg of drug diluted with 0.9% saline 10ml IV, Group L (Labetalol) were given 0.4mg/kg of the drug diluted with 0.9% saline 10ml IV. All the patients were subjected to the same anaesthesia technique. HR, SBP, DBP, MAP, RPP were recorded prior to intubation, then 0 minute, 2 min, 3 min and up to 5 min post intubation. **Results:** Compared to esmolol, labetalol significantly attenuated HR, SBP, DBP, MAP and RPP during laryngoscopy and intubation. **Conclusion:** Labetalol is a better agent than esmolol in attenuating the sympathomimetic response to laryngoscopy and intubation.

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

INTRODUCTION

Laryngoscopy and endotracheal intubation are noxious stimuli that may induce profound changes in cardiovascular physiology, primarily through reflex responses. The cardiovascular responses to airway manipulation are initiated by proprioceptors responding to tissue irritation in the supraglottic region and in the trachea.[1] These proprioceptors consist of mechanoreceptors with small-diameter myelinated fibers, slowly-adapting stretch receptors with large-diameter myelinated fibers, and polymodal endings of non-myelinated nerve fibers.[2] The glossopharyngeal and vagal afferent nerves transmit these impulses to the brainstem, which, in turn, causes widespread autonomic activation through the sympathetic and parasympathetic nervous systems.

The more common response to airway manipulation is hypertension (HTN) and tachycardia mediated by the cardioaccelerator nerves and sympathetic chain ganglia. This response includes widespread release of norepinephrine from adrenergic nerve terminals and secretion of epinephrine from the adrenal medulla.[3] Patients with cardiovascular or cerebral disease may be at increased risk of morbidity and mortality from the tachycardia and hypertension resulting from this stress.[4]

There are many methods to attenuate these responses like increasing the concentration of volatile anaesthetic agents during mask ventilation before intubation or premedicating the patient with drugs like intravenous lignocaine, selective and non-selective beta blockers, selective and non-selective alpha-blockers, alpha-2 agonists (clonidine and Dexmedetomidine), ACE inhibitors, Gabapentin, calcium channel blockers, $MgSo_4$, Opioids and non-narcotic pain relievers.[5-9]

The present study was designed to study the effectiveness of Labetalol (0.4mg/kg) and Esmolol (1.5mg/kg) in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation in patients undergoing surgical procedures under general anaesthesia.

AIMS OF THE STUDY

To compare the efficacy of esmolol 1.5mg/kg and labetalol 0.4mg/kg for attenuation of sympathomimetic response to laryngoscopy and intubation.

MATERIALS AND METHODS

In this study, 60 healthy adult normotensive patients of ASA class 1 or 2 between age group of 18-45 years, weighted between 40-65 kg undergoing elective surgical procedure under general anaesthesia that required

orotracheal intubation were selected. Comparative observational study was carried out after approval from institutional ethical and scientific review committee.

A detailed history was taken and the patients were thoroughly examined on the previous day of surgery. The procedure was explained and written informed consent was taken from the patients prior to surgery.

Following patients were excluded from the study:

- Past or present history of hypertension (BP of 140/90mmHg)
- Impaired cardiovascular, respiratory, renal or hepatic dysfunction
- Hypotension (MAP of 80mmHg)
- Bradycardia (PR of 50/min)
- Patients with predicted difficult intubation.

Patients were kept nil per orally for 8 hours prior to surgery. Intravenous line was started with RL pint.
Heart rate, systolic, diastolic and mean arterial blood pressure, rate pressure product (RPP) was recorded just prior to premedication and was taken as the baseline.

Premedication: (10 minutes before induction)

- Inj.Glycopyrrolate 0.2mg i.v
- Inj.Midazolam 0.04mg/kg i.v
- Inj.Ondansetron 0.1mg/kg i.v

The patients were randomly and equally allocated in two groups by computer generated random numbers:
Group E: i.v Esmolol 1.5mg/kg (dilution with 0.9% NS to 10ml) 2 minutes prior to intubation.

Group L: i.v Labetalol 0.4mg/kg (diluted with 0.9% NS to 10ml) 5 minutes Prior to intubation.

Continuous monitoring of ECG was done. Heart rate, systolic, diastolic and mean arterial blood pressure, rate pressure product (RPP) was recorded after giving the study drug.

Induction, Maintenance and Recovery from anaesthesia:

- Patients were pre-oxygenated with 100% oxygen for three minutes.
- Study drug was given as mentioned above.
- The patients were induced with 2.5% sodium thiopentone till the eyelash reflex was lost, followed by succinylcholine 1.5mg/kg i.v to facilitate tracheal intubation
- After the disappearance of fasciculation, laryngoscopy and intubation was done using standard Macintosh laryngoscope.
- Patients were then ventilated with 50% N_20 in 50% 0_2.
- All intubations were completed within 15 seconds. Cases in which intubation required more than 15 seconds were excluded from the study.
- Immediately after tracheal intubation; heart rate, systolic, diastolic and mean arterial blood pressure, rate pressure product (RPP) were recorded as 0 min. These readings were repeated at intervals of 2, 3, and 5 min from the 0 min reading.
- After 5 min, administration of volatile inhalational agent was started. Patients were maintained on inhalational agent and a non-depolarizing muscle relaxant as per the need of the surgical procedure.
- At the end of surgery residual neuromuscular block was antagonized with Inj. Neostigmine 50µg/kg i.v & Inj. Glycopyrrolate 10µg/kg i.v.

➢ Patients were observed for any side effects like hypotension, bradycardia, arrhythmias and bronchospasm during the intraoperative period.

The results were expressed as mean ± SD. Statistical analysis was done using paired t-test and p value less than 0.05 was considered as significant.

OBSERVATION AND RESULTS

The patients in the both groups were comparable with respect to age, weight and sex distribution (Table 1).

In this study of 60 patients, 32 patients were posted for general surgery, 19 patients were posted for ENT surgery, 7 were posted for gynaecological surgery and 2 patients were posted for orthopaedic surgery (Table 2).

Baseline reading of mean heart rate was comparable in both groups. There was No significant difference in heart rate before induction and after study drug among the groups. At the time of laryngoscopy, the rise from the pre-induction value was seen in both the groups. On comparing both groups, mean heart rate was Low in Group L as compared to group E. This difference was statistically significant. At 2 and 3 minutes after intubation, the rise in heart rate from pre-induction value was statistically significant in Group E. Heart rate returned to pre induction value at 3rd minute in Group L. At 5 minutes after intubation the heart rate returned to pre-induction value in group E and mean heart rate fell below baseline in group L (Table-3).

Baseline reading of mean systolic blood pressure was comparable in both groups. There was No significant difference in systolic blood pressure before induction and after study drug among the groups. At the time of laryngoscopy, the rise from the pre-induction value was seen in both the groups. On comparing both groups, mean systolic blood pressure was Low in Group L as compared to group E. This difference was statistically significant. At 2 and 3 minutes after intubation, the rise in systolic blood pressure from pre-induction value was statistically significant in Group E. Systolic blood pressure returned to pre induction value at 3rd minute in Group L. At 5 minutes after intubation the systolic blood pressure returned to pre-induction value in group E and

mean systolic blood pressure fell below baseline in group L (Table-4).

Baseline reading of mean diastolic blood pressure was comparable in both groups. There was No significant difference in diastolic blood pressure before induction and after study drug among the groups. At the time of laryngoscopy, the rise from the pre-induction value was highly significant in both the groups. On comparing both groups, mean diastolic blood pressure was Low in Group L as compared to group E. This difference was statistically insignificant. At 2 and 3 minutes after intubation, the rise in diastolic blood pressure from pre-induction value was statistically significant in both the groups. At 5 minutes after intubation the diastolic blood pressure returned to pre-induction value in both the groups (Table-5).

Baseline reading of mean arterial pressure was comparable in both groups. There was No significant difference in mean arterial pressure before induction and after study drug among the groups. At the time of laryngoscopy, the rise from the pre-induction value was seen in both the groups. On comparing both groups, MAP was Low in Group L as compared to group E. This difference was statistically significant. At 2 and 3 minutes after intubation, the rise in MAP from pre-induction value was statistically significant in Group E. MAP returned to pre induction value at 3rd minute in Group L. At 5 minutes after intubation the MAP returned to pre-induction value in group E and MAP fell below baseline in group L (Table-6).

Baseline reading of rate pressure product was comparable in both groups. There was No significant difference in RPP before induction and after study drug among the groups. At the time of laryngoscopy, the rise from the pre-induction value was seen in both the groups. On comparing both groups, RPP was Low in Group L as compared to group E. This difference was statistically significant. At 2 and 3 minutes after intubation, the rise in RPP from pre-induction value was statistically significant in Group E. RPP returned to pre induction value at 3rd minute in Group L. At 5 minutes after intubation the RPP returned to pre-induction value in group E and RPP fell below baseline in group L (Table-7).

Adverse effects

In our study, No major complications like hypotension, bradycardia, bronchospasm, arrhythmias or ischemic changes were found in any patients in both the groups.

Table 1: Demographic Data.

Parameters	Group E	Group L
Age (yrs)	28.3±7.9	29.9±6.7
Weight (kg)	54.2±5.8	52.7±6.1
Male/Female	17/13	12/18

Table 2: Types of surgery.

Type of surgery	Group E		Group L	
	No. of patients	%	No. of patients	%
General surgery	16	53.5	16	53.5
ENT surgery	10	33.5	9	30
Gynaecological surgery	3	10	4	13.5
Orthopaedic surgery	1	3	1	3

Table 3: Changes in heart rate.

Time Interval	Group E		Group L	
	Mean	SD	Mean	SD
A	80.1	7.42	82.03	6.31
B	82.76	7.23	83.66	6.26
C	83.13	6.47	84.16	5.97
D+0	96.20	6.84	90.03	6.38
D+2	98.40	6.14	91.63	6.37
D+3	89.86	5.5	84.03	5.83
D+5	82.03	4.9	75.46	4.93

Time Intervals - A: Baseline, B: after premedication (before induction), C: after study drug, D+0: during laryngoscopy and intubation, D+2,3,5 :2,3,5 minutes after intubation.

Table 4: Changes in systolic blood pressure.

Time Interval	Group E		Group L	
	Mean	SD	Mean	SD
A	122.86	5.16	123.46	4.36
B	124.16	4.72	124.03	4.26
C	124.76	4.48	124.56	4.15
D+0	140.56	5.53	130.13	4.59
D+2	145.23	5.46	133.23	5.17
D+3	137.03	5.24	124.20	4.48
D+5	123.80	4.89	116.23	4.47

Time Intervals - A: Baseline, B: after premedication (before induction), C: after study drug, D+0: during laryngoscopy and intubation, D+2,3,5 :2,3,5 minutes after intubation.

Table 5: Changes in diastolic blood pressure.

Time Interval	Group E		Group L	
	Mean	SD	Mean	SD
A	80.70	2.78	80.70	2.64
B	81.33	2.63	81.36	2.39
C	81.63	2.42	81.53	2.43
D+0	98.26	3.31	95.86	2.73
D+2	90.30	2.65	88.63	2.47
D+3	86.00	2.49	85.46	2.28
D+5	82.16	2.35	81.56	2.34

Time Intervals - A: Baseline, B: after premedication (before induction), C: after study drug, D+0: during laryngoscopy and intubation, D+2,3,5 :2,3,5 minutes after intubation.

Table 6: Changes in mean arterial pressure.

Time Interval	Group E		Group L	
	Mean	SD	Mean	SD
A	94.75	3.51	94.95	3.11
B	95.61	3.25	95.54	2.91
C	96.12	3.02	95.87	2.88
D+0	112.70	3.95	109.28	2.23
D+2	108.27	3.43	102.83	2.36
D+3	103.01	3.22	96.37	1.70
D+5	96.14	3.10	93.38	1.92

Time Intervals - A: Baseline, B: after premedication (before induction), C: after study drug, D+0: during laryngoscopy and intubation, D+2,3,5 :2,3,5 minutes after intubation.

Table 7: Changes in rate pressure product.

Time interval	Group E		Group L	
	Mean	SD	Mean	SD
A	9838.80	979.91	10134.00	940.45
B	10402.30	998.14	10385.23	964.25
C	10651.83	917.31	10528.63	926.94
D+0	14233.27	1228.65	11984.73	1055.82
D+2	15673.67	1202.02	12874.40	1100.03
D+3	12869.03	998.59	10575.27	913.82
D+5	10463.23	838.61	8773.70	699.71

Time Intervals - A: Baseline, B: after premedication (before induction), C: after study drug, D+0: during laryngoscopy and intubation, D+2,3,5 :2,3,5 minutes after intubation.

DISCUSSION

There has been a constant search among anaesthesiologists to find an ideal agent to attenuate the intubation response. **Chung F and McCammon R. L** observed that laryngoscopy was responsible for rise in arterial pressure and tracheal intubation caused rise in heart rate.[10,11] This is consistent with our study where maximum rise in BP occurred immediately after intubation and HR was highest at 0 min post-intubation**. Forbes AM** stated that HR and BP returned to pre-laryngoscopy level in normotensives within 5 minutes due to adaptation and gradual fatigue of receptors, cessation of stimulus and deepening of anaesthesia.[12]

Stimulus of the laryngeal and tracheal tissues may also cause increase in both sympathetic and sympathoadrenal reflex activity (**Kovac; Prys-Roberts et al**).[13,14] Different pharmacologic agents like lidocaine, vasodilator agents inhibiting sympathoadrenal response, α and β adrenergic blockers, and opioids can be administered prior to tracheal intubation in order to prevent haemodynamic responses **(Helfman et al; Mikawa et al)**.[5,15] However, studies comparing esmolol (cardio-selective beta blocker) and labetalol (non-selective adrenergic blocker) are very few.

Esmolol is an ultra short acting β1 cardio selective, β blocking agent with a short half-life and its onset of action is very prompt. This is an ideal drug to keep the hemodynamic reflex during intubation under control. On the other hand, labetalol has an onset of action 5 minutes, and has also emerged as a possible drug of choice for hemodynamic reflex attenuation during intubation. 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 generally described benefit of labetalol is that apart from attenuating the response to laryngoscopy and intubation, it also prevents perioperative cardiovascular events **(Kim et al.; Chung et al; Inada et al; Ramnathan et al).**[16-19]

Labetalol had a significantly (P<0.05) better effect than esmolol in controlling PR at all points during the study. It seems that when instrumentation stimulus is present labetalol maintains the PRs within normal ranges (Table 3). When the effect of stimulus weans off, as occurs at 5 minutes post-intubation, the drug`s effect takes over and pulse rates go below baseline values. **Shribman and Smith et al** showed that the plasma catecholamine concentration came down by 3 minutes to 5 minutes after the laryngoscopy.[1]

Labetalol prevented the increase in SBP significantly throughout the study period as compared to esmolol group (P<0.05) (Table 4). **Ramanathan *et al*** used 20 mg labetalol to prevent rise in SBP successfully.[19] **Inada *et al*** found 10 mg (0.14 mg/kg) labetalol ineffective in attenuating the rise in systolic pressure.[18] 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 was lost at intubation.

There was no significant difference between values of Esmolol and Labetalol during laryngoscopy and up to 5 minutes after that (p>0.05) (Table 5). Our findings correlates with findings of **Inda et al**. (labetalol 10 mg), **Benstein et al**. (Labetalol 0.25mg/kg), **Chung KS et al**.(0.4 mg/kg) and **Maharaj et al**. (Labetalol 0.25 and 0.5 mg/kg) who failed to attenuate the rise in diastolic blood pressure.[18,21,16,22] Esmolol even in doses exceeding > 1 mg/kg have been found to be ineffective in controlling diastolic pressure rise which correlate with studies of **Sarvesh P Sing et al., Sowbhagya Laxmi et al.**[23,24] Values of DBP return to baseline 5 minutes after laryngoscopy and intubation in both the groups.

After intubation (0 Min) there is maximum increase in mean arterial pressure with both Esmolol group and labetalol group. This observation is the same as made by **SP singh *et al***[23] and **Sharma *et al*** [25] in their studies, although esmolol was not at all effective in controlling MAP rise after laryngoscopy and intubation. The labetalol group showed better attenuation of mean arterial pressure than Esmolol group which was statistically highly significant (p < 0.001). Mean arterial pressure returned to normal baseline values at 5th minute

in esmolol group. In labetalol group, the mean arterial pressure fell below the baseline in 5th minute (Table-6).

The labetalol group had significantly lower values of RPP. Labetalol could not prevent the increase in RPP completely (significantly elevated at 0 min post-intubation). This observation is the same as made by **SP singh *et al.*** [23] However, the magnitude of increase was less and never crossed the critical limit of 15,000. RPP returned to normal baseline values at 5th minute in esmolol group. In labetalol group, the RPP fell below the baseline in 5th minute (Table-7). Therefore, labetalol (0.4 mg/kg) decreases the magnitude and duration of hemodynamic response to laryngoscopy as evident from changes of RPP. **Leslie *et al*.** 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.[26]

No major complications like hypotension, bradycardia, bronchospasm, arrhythmia or ischemic changes were found in any patients in both the groups.

CONCLUSION

On the basis of the findings of the study, we conclude that Labetalol in doses of (0.4 mg/kg) is better agent than esmolol (1.5mg/kg) in attenuating the sympathomimetic response to laryngoscopy and intubation. Further studies are recommended to substantiate the findings in the present study.

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