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A CLINICAL COMPARATIVE STUDY OF ESMOLOL VERSUS COMBINATION OF ESMOLOL AND FENTANYL IN ATTENUATING THE HAEMODYNAMIC STRESS RESPONSE TO INTUBATION

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ABSTRACT

Aim and Objectives- The aim of this study was to compare the effect of intravenous Esmolol versus combination of intravenous Esmolol and Fentanyl in attenuating the haemodynamic stress response to intubation.

Methods: After taking ethical committee clearance, a prospective randomised double blinded study involving 80 patients aged 20-60 years of either sex and ASA physical atatus I or II are scheduled for elective surgeries under general anaesthesia were randomly placed into two groups. Group A- Esmolol 1.5mg/kg intravenously given 5 minutes prior to induction and, Group B- Esmolol 1.5mg/kg & Fentanyl 2µg/kg intravenously given 5 minutes prior to induction.

Results: There was no significant difference in HR, SBP , DBP and MAP after premedication between both the groups. There was no significant difference in HR, SBP immediately after induction but significant difference was seen in DBP and MAP . However at intubation both the groups showed an increase in HR, SBP, DBP and MAP but it was attenuated in both the groups. The increase was seen more in group A than in group B. The increase in HR was statistically significant at 1 mins post intubation. The increase in SBP was statistically significant during intubation, at 1min and 2 mins post intubation. The increase in DBP and MAP was statistically significant immediately after induction, during intubation, at 1min post intubation and 2 mins post intubation.

Conclusions: Combination of esmolol 1.5 mg/kg and fentanyl 2µg/kg was more effective than inj. Esmolol 1.5mg/kg alone in attenuating the haemodynamic stress response to intubation.

INTRODUCTION

Laryngoscopy and endotracheal intubation is an important part of general anaesthesia. It is a safest and gold standard method for establishing a definitive airway.

The circulatory response to laryngeal and tracheal stimulation were known since 1940 after its description by Reid and Brace.[1] In 1951, King et al described the circulatory responses to endotracheal intubation as reflex sympathoadrenal stimulation.[2]

Direct laryngoscopy and endotracheal intubation is almost always associated with haemodynamic changes due to reflex sympathetic discharge which is caused by the epipharyngeal and laryngopharyngeal stimulation.[3] This results in increase in blood pressure and heart rate due to sympathoadrenal activity.[4,5]

Even though the increase in blood pressure and heart rate due to laryngoscopy and intubation may be brief, they may have a hazardous effects in high risk patients with hypertension, myocardial insufficiency and cerebrovascular diseases. Various methods and drugs have been tried to attenuate these deleterious effects.

Among the beta adrenergic antagonist, Esmolol has been an effective drug due to its cardioselective adrenergic receptor blocking properties. It is an ultra short acting drug. It has an alpha distribution half life of 2 minutes and beta distribution half life of 9 minutes. Hence it has been used in attenuating the haemodynamic stress response to intubation.

Opiods have been also used in attenuating the haemodynamic stress response to intubation as it improves haemodynamic stability, lowers requirement for other anaesthetic agents, reduces preoperative anxiety and pain and minimizes post-operative pain. Fentanyl is a synthetic opiod derivative and potent analgesic which is 100 times more potent than morphine. It predominately act as an agonist on mu(µ) receptors.

The present study was undertaken to study clinically the effects of beta adrenergic blocker esmolol and combination of esmolol and fentanyl in attenuating the haemodynamic stress response to intubation.

MATERIALS AND METHOD

A study was undertaken after obtaining Institutional Ethical Committee clearance and written informed consent from the patients. A prospective randomized double blinded study involving 80 patients of both sexes requiring endotracheal intubation and general anaesthesia for various elective surgical procedures belonging to ASA grade I and II were included in the study. The study population was divided into 2 groups with 40 patients in each group.

Group A: Esmolol 1.5mg/kg intravenously given 5 minutes prior to induction.

Group B: Esmolol 1.5mg/kg & Fentanyl 2µg/kg intravenously given 5 minutes prior to induction.

Patient with anticipated difficult airway, ASA grade III &IV, history of drug allergy to study drug, pregnant and lactating mother, patient with any disorders of cardiovascular system, respiratory system, renal system, hepatic and neuromuscular conditions, emergency surgery, patient's refusal, laryngoscopy time > 30 secs or more than one attempt for intubation were excluded excluded from the study.

On the day of surgery, after confirmation of NPO status, patients were shifted to the operating room and connected to multipara monitor for continuous monitoring. The baseline pulse rate, spo2, systolic and diastolic pressure, mean arterial pressure, respiratory rate were recorded. An I.V line was secured with appropriate sized cannula and i.v fluids were started with 500ml of Ringer's lactate in all patients. All patients were premedicated with inj. ranitidine 50mg I.V, inj.Ondansetron 4mg I.V and inj.Glycopyrolate 0.2 mg I.V, inj midazolam 0.02mg/kg 15 mins prior to induction. Study drugs were given 5 minutes before induction. Preoxygenation with

100% oxygen was done for 3 minutes with facemask of appropriate size . Induction done with inj. Propofol 2mg/kg and muscle relaxation achieved with succinylcholine 1.5mg/kg.

Endotracheal intubation was accomplished within 15 seconds in all patients. Anaesthesia was maintained with mixture of N2O and O2 gas at 66% and 33% respectively along with isoflurane. Muscle relaxation was maintained with initial dosage of inj. Atracurium 0.3 mg/kg I.V and then with one-fourth of the initial dose.

The following parameters like heart rate, systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial pressure(MAP) and SPO2 and EtCO2 were noted as follows- baseline reading (T0), premedication +10 minutes (T1)-immediately after induction (T2)-during intubation (T3)-1 minute post intubation (T4)-2 minutes post intubation (T5)- 5 minutes post intubation (T6)-10 minutes post intubation (T7) - 30 minutes post intubation (T8)-60 mins post intubation (T9)

At the end of surgery, when patients had respiratory efforts, residual neuromuscular blockade was reversed with Inj Neostigmine 0.05 mg/kg i.v. & Inj. Glycopyrrolate 0.01 mg/kg i.v. Recovery assessement & extubation were done after thorough laryngeal suction.

Post Operatively:
The patients were shifted to the post op. ward, and the pulse rate, systolic blood pressure, diastolic blood pressure, side effects (if any) were recorded at every 30mins interval till 120 mins and thereafter at 1 hour interval till 6 hours period after post operatively.

STATISTICAL METHOD EMPLOYED
All data were presented as Mean ± SD (Standard Deviation). All Quantitative data were assessed using t-test to analyze changes over a period of time. Qualitative data are assessed using Chi- square test.

- p>0.05 – Statistically Not Significant (NS)
- p<0.05 – Statistically Significant (S)
- p<0.001 – Statistically highly Significant (HS)
- p<0.0001 - Statistically Extremely Significant (ES)

STATISTICAL SOFTWARE EMPLOYED
The statistical software **SPSS** was used for the analysis of data and **Microsoft Word** and **Microsoft Excel** had been used to generate graphs, tables etc.

RESULTS
The present study consisted of 80 patients who were divided into 2 groups of 40 each; where Group A has received inj. Esmolol 1.5mg and Group B received inj. Esmolol 1.5mg and Fentanyl 2µg/kg given 5 mins prior to induction in separate syringes.

Demographic variables
Table 1: Demographic data and ASA grading

	Group A	Group b	p-value
Age (years)	35.82±9.39	33.67±8.05	0.27(NS)
Gender (M/F)	19/21	20/20	0.823(NS)
Weight (kg)	57.575±8.44	57.10±8.49	0.82(NS)
ASA (I/II)	30/10	28/12	0.617(NS)

From Table 1,there was no statistically significant difference between the groups regarding demographic profile and ASA grading.

Haemodynamic variables
Table 2: Baseline parameters

Parameter	Mean± SD		p-value
	Group A	Group B	
Heart Rate(beats/min)	82.85±10.32	80.85±7.79	0.759(NS)
SBP	123.65±6.9	123.95±6.31	0.84(NS)
DBP	74.22±4.85	73.22±3.83	0.62(NS)
MAP	89.97±4.36	88.67±4.19	0.178(NS)

From Table 2, the baseline parameters between two groups were statistically similar with p-value >0.05 (NS).

Table 3: Changes in HR (beats/min)

Time Interval	Group A		Group B		p-value
	Mean	SD	Mean	SD	
T0	82.85	±10.32	80.85	±7.79	0.759 (NS)
T1	79.12	±7.05	80.20	±6.68	0.48 (NS)
T2	79.07	±6.15	79.48	±7.95	0.79 (NS)
T3	91.75	±10.13	90.40	±7.03	0.49 (NS)
T4	90.025	±5.735	87.50	±4.15	0.025 (S)
T5	88.125	±4.54	85.375	±4.86	0.0035(NS)
T6	87.75	±5.73	85.15	±3.43	0.076 (NS)
T7	86.60	±4.60	84.82	±4.76	0.097(NS)
T8	84.07	±5.89	82.30	±7.99	0.26 (NS)
T9	82.725	±4.75	80.70	±6.95	0.134 (NS)

From Table 3, it was observed that there was no significant increase in heart rate after premedication+ 10mins (T1) and immediately after induction (T2) in both the groups. But during intubation (T3), 1min post intubation(T4), 2mins post intubation (T5), both groups showed increase in heart rate. The difference in both the groups was statistically significant at 1 post intubation. The rise in HR was seen more in group A than in group B.

Table 4: Changes in SBP (mmHg)

TIME INTERVAL	GROUP A		GROUP B		P-VALUE
	MEAN	SD	MEAN	SD	
T0	123.65	±6.9	123.95	±6.31	0.84(NS)
T1	122.9	±7.43	121.075	±7.11	0.26(NS)
T2	112.05	±5.53	109.825	±6.63	0.107(NS)
T3	138.57	±6.69	134.025	±3.77	<0.0001(ES)
T4	134.175	±5.03	130.15	±3.23	<0.0001(ES)
T5	131.20	±4.53	127.15	±3.60	<0.0001(ES)
T6	127.50	±3.60	126.15	±3.95	0.114(NS)
T7	125.30	±2.79	124.30	±5.72	0.325(NS)
T8	124.12	±6.18	123.15	±6.02	0.47(NS)
T9	123.32	±3.10	123.625	±4.20	0.83(NS)

From table 4, it was observed that SBP was significantly lower than baseline in both the groups immediately after induction (T2). However, both the groups showed increase in SBP during intubation (T3), 1 min post intubation (T4) and 2 mins post intubation (T5) which were statistically significant. The rise in SBP was seen more in group A than in group B.

Table 5 : Changes in DBP (mmHg)

TIME INTERVAL	GROUP A		GROUP B		P-VALUE
	MEAN	SD	MEAN	SD	
T0	74.22	±4.85	73.22	±3.83	0.62(NS)
T1	73.92	±4.69	72.95	±3.65	0.29(NS)
T2	68.25	±2.25	63.75	±3.75	<0.0001(ES)
T3	86.55	±3.28	82.25	±4.67	<0.0001(ES)
T4	84.02	±3.76	78.21	±4.59	<0.0001(ES)
T5	81.15	±3.12	76.75	±4.59	<0.0001(ES)
T6	71.72	±4.09	71.47	±4.12	0.24(NS)
T7	70.02	±3.53	71.05	±2.83	0.32(NS)
T8	69.80	±3.49	72.35	±2.83	0.11(NS)
T9	72.27	±2.18	73.27	±3.32	0.12(NS)

From Table 5, it was observed that there was fall in DBP from baseline immediately after induction in both the groups which was statistically significant. However, there was increase in DBP during intubation (T3), 1 min post intubation (T4) and 2 mins post intubation (T5) which were statistically significant. The rise in DBP was seen more in group A than in group B.

Table 6: Changes in MAP (mmHg)

Time Interval	Group A		Group B		p-value
T0	89.97	±4.36	88.67	±4.19	0.178(NS)
T1	89.52	±4.20	88.25	±3.95	0.158(NS)
T2	84.10	±3.83	80.15	±4.16	<0.0001(ES)
T3	102.65	±3.25	98.20	±4.58	<0.0001(ES)
T4	100.52	±3.34	95.07	±3.45	<0.0001(ES)
T5	92.70	±4.32	90.20	±3.69	<0.0001(ES)
T6	89.17	±4.43	88.55	±4.94	0.553(NS)
T7	87.85	±4.71	87.35	±3.59	0.103(NS)
T8	87.40	±4.28	87.25	±3.25	0.108(NS)
T9	88.20	±3.30	88.42	±4.48	0.25(NS)

From Table 6, it was observed that the MAP was lower than baseline immediately after induction (T2) in both the groups which was statistically significant. However, there was increase in MAP during intubation (T3), 1 min post intubation (T4) and 2 mins post intubation (T5) in both the groups which were statistically significant. The rise in MAP was seen more in group A than in group B.

DISCUSSION

Endotracheal intubation and laryngoscopy causes increase in blood pressure and heart rate and occasionally arrhythmias[6]. These effects usually occur briefly and thus they are tolerated well by overall healthy patients but not in patients with co-morbid conditions.

Many agents have been used to attenuate the these undesirable haemodynamic responses to laryngoscopy and intubation with varying success. These includes opiods, [7-9] beta blockers, [10-12] lignocaine, [13,14] calcium channel blockers, [15-17] vasodilators, [18-20] used alone or in combination with other drugs.

The present study was aimed at comparing intravenous esmolol and combination of esmolol and fentanyl in attenuating the haemodynamic stress response to intubation. The study population consisted of 80 patients divided equally in two groups. Patients in group A received inj. Esmolol 1.5mg/kg body weight /iv 5 mins prior to induction and patients in group B received inj. Esmolol 1.5mg/kg body weight /iv and inj. Fentanyl 2µg/kg body weight/iv, 5 minutes prior to induction.

The mean age, weight, height, sex, of both the groups were comparable. There was no significant difference between the groups with regard to demographic variables (p value >0.05). In our study, HR was found to be significant at 1 min post intubation(T4). SBP was found to be significant during intubation (T3), 1 min post intubation (T4) and 2 mins post intubation(T5).

DBP and MAP were found to be significant after induction (T2), during intubation (T3), 1 min post intubation (T4) and 2 mins post intubation (T5).

Similar findings were also observed on several studies done by **Bhalke et al ,** [21] **Chung et al,** [22] **Dr Parth et al,** [23] and **Donald R Miller** [24].

SIDE EFFECTS

In our study post operative nausea and vomiting were noticed in 2.5% patients in group A and in 5% patients in group B. These side effects didn't require any intervention.

Bhalke et el, [21] studied the haemodynamic response to intubation using esmolol and esmolol and fentanyl combination and noticed 6.67% incidence of post operative nausea and vomiting in esmolol alone and 10% incidence in esmolol and fentanyl combination.

No other side effects were seen.

CONCLUSION

Combination of esmolol 1.5 mg/kg and fentanyl 2µg/kg was more effective than inj. Esmolol 1.5mg/kg alone in attenuating the haemodynamic stress response to intubation.

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