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COMPARISON OF ESMOLOL, CLONIDINE, AND LIGNOCAINE FOR SUPPRESSION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION AS AN ADJUVANT TO FENTANYL IN ADULT PATIENTS UNDERGOING ELECTIVE SURGERY

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ABSTRACT **Introduction:** Laryngoscopy and endotracheal intubation lead to a strong sympathetic response, this study was done to compare clonidine, esmolol, and lignocaine as an adjuvant to fentanyl to attenuate the pressor response to laryngoscopy during endotracheal intubation. **Objectives:** To compare clonidine, esmolol, and lignocaine as an adjuvant to fentanyl to attenuate the pressor response to laryngoscopy during endotracheal intubation. **Material and Methods:** A Randomized prospective study including 150 normotensive patients undergoing elective surgical procedures were included. Three groups were divided according to drug they received. After 3 minutes of drug , laryngoscopy and endotracheal intubation were done. Vitals (HR,SBP,DBP and MAP) were noted before laryngoscopy and endotracheal intubation and 1,2,4,6 and 8 minute after Laryngoscopy and endotracheal intubation and anaesthesia was continued with O2+N2O+Sevoflurane. **Results:** Rise in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) at one minute following intubation in all three groups of drugs ($p<0.001$). SBP both esmolol and clonidine reached equal to baseline in 4 mins with their respective p-value as 0.293 and 0.097 and group lignocaine reached equal to baseline in 6 mins. DBP of group esmolol reached baseline at 4 mins (p-value- 0.090), group clonidine reached baseline in 6 mins. And group lignocaine does not reach baseline even after 8 mins. MAP in esmolol group reached to baseline in 4 mins, group clonidine reached to baseline in 6 mins and group lignocaine does not reach to baseline even after 8 mins. **Conclusion:** Considering all parameters, it was concluded that esmolol with fentanyl showed better response on all parameters.

KEYWORDS : Clonidine ,Esmolol, Lignocaine, Pressor response, Tracheal intubation

Introduction:

Airway management is the core skill of the anaesthetist, and various airway management techniques have developed over many years. Unfortunately, laryngoscopyand intubation can result in physiological and pathophysiological reflex responses. The pressor response to laryngoscopy and endotracheal intubation was recognized and documented In 1940 by Reid and Brace.[1] In anaesthesia practice, the severe hemodynamic response to laryngoscopy and endotracheal intubation had been a significant concern, and several methods and interventions are described to attenuate these responses. The goal of tracheal intubation is to provide a secure airway. Laryngoscopy and endotracheal intubation lead to a solid sympathetic response which manifests as transient but marked tachycardia and hypertension.[2] These responses are initiated by stimulation of afferent receptors in the posterior pharynx supplied by the glossopharyngeal and vagus nerves. The central nervous system (CNS), cardiovascular system, and respiratory system all respond predictably to these afferent stimuli, in selected patients, the resultant physiologic manifestations may adversely affect the patient'soutcome. This response is maximum immediately following intubation and lasts for 5-10 minutes. It may precipitate the increases in intracranial pressure (ICP), arrhythmias, myocardial ischemia, and cardiovascular accidents in a patient with preexistingcardiovascular disease.[3,4] The mechanism of this response to laryngoscopy and endotracheal intubation is proposed to be by somato visceral reflexes. Stimulation of proprioceptors at the base of the tongue during laryngoscopy induces impulse dependent increase of systemic blood pressure, heart rate, and plasma catecholamine concentration. 2,3,4. In children, this is due to a monosynaptic reflex that promotes vagal stimulation of the sinoatrial node, resulting in bradycardia. In adults, this is due to polysynaptic event predominates whereby impulses travel afferently via the 9th and 10th cranial nerves to the brain stem and spinal cord. An efferent sympathetic response results in norepinephrine release from adrenergic nerve terminals, epinephrine release from the adrenal glands, and activation of the renin-angiotensin system leading to tachycardia and hypertension. These responses may be detrimental in patients with myocardial ischemia (tight heart), known intracerebral or aortic aneurysms, major vessel dissection, or those with major vascular injuries. Laryngoscopy and endotracheal intubation result in stimulation of the central nervous system,as evidenced by increases in electroencephalographic (EEG) activity, cerebral metabolic rate,and cerebral blood flow (CBF). [4] In patients with compromised intracranial compliance, the increase in CBF may result in elevated intracranial pressure (ICP), which results in herniation of brain contents and severe neurologic compromise. Intracranial aneurysms and arteriovenous malformations (AVMs) often arise with a small “sentinel” hemorrhage. During subsequent periods of elevated arterial BP, these lesions are likely to rebleed, resulting in sudden and permanent neurologic injury. Many neurosurgeons and interventional neuroradiologists attempt to stabilize cerebral aneurysms and AVMs soon after hospitalization to minimize the risk of rebleeding. This means that the patient presents for anaesthesia at a time when the clot tamponading the aneurysm or AVM is particularly delicate, and a small increase in arterial transmural pressure could cause rupture. One of the times at which this is most likely to occur is when the arterial BP and the HR are increased in response to endotracheal intubation.[5]Therefore, neurosurgical anaesthesiologists pay meticulous attention to attenuating these responses during anaesthetic induction and endotracheal intubation.Several drugs have been used to attenuate these adverse responses, including intravenous local anaesthetics, opioids, calcium channel blockers, clonidine, gabapentin, and β -adrenergic blockers (esmolol and metoprolol). In view of that, the objective of our study is to compare clonidine, esmolol, and lignocaine as an adjuvant to fentanyl to attenuate the pressor response to laryngoscopy during endotracheal intubation.For safe conduct of anaesthesia, the pressor response to laryngoscopy and endotracheal intubation should be blunted. To compare clonidine, esmolol, and lignocaine as an adjuvant to fentanyl to attenuate the pessor response to laryngoscopy during endotracheal intubation.

Material and Methods:

This randomized prospective study was conducted at Metro heart institute and multispeciality, Faridabad, Haryana after obtaining hospital ethical committee clearance and informed consent from all patients. 150 normotensive patients of the American Society of an anaesthesiologist (ASA) grade 1 and 2 aged between 18-65 years underwent elective surgical procedures were included in our study. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients in their language for inclusion in the study. Patients with an anticipated difficult airway, who would require more than one attempt for intubation and ASA grade 3 and 4 were excluded from this study, other exclusion criteria were pregnancy, obese patients (BMI > 30) and known hypersensitivity to drugs, and patients refusal to give consent for the study. All patients were examined during the pre-op visit and they were investigated as required based on patient status.The patient werecounselled and consent was taken followed by requiredfasting.

150 patients were divided into three groups. 50 patients receivedinj clonidine intravenously15 minutesbeforeinduction, 50 patients

receivedinj lignocaine intravenously 3 minutes before induction and 50 patients receivedinjesmolol intravenously 3 minutes before induction. In the preoperative room, preoperative vitals were checked. On arrival to the operating room, baseline vitals were checked (HR, SBP, DBP, MAP) and was preoxygenated with 100% oxygen for three minutes followed by premedication which contains InjEmset 0.01mg/kg, Inj Midazolam 0.03mg/kg, and Inj Fentanyl 2mcg/kg. Group clonidine receivedInj clonidine 1.5mcg/kg, Group lignocaine received Inj lignocaine 1.5mg/kg and group esmolol receivedInj esmolol 1.5 mg/kg. After this vitals was monitored and induction was started by Injpropofol 2mg/kg and after checking ventilation injvecuronium(0.1mg/kg) was administered. After 3 minutes laryngoscopy and endotracheal intubation were done. Vitals (HR,SBP,DBP and MAP) were noted before laryngoscopy and endotracheal intubation and 1,2,4,6 and 8 minute after Laryngoscopy and endotracheal intubation and anaesthesia was continued with O_2+N_2O+Sevoflurane.

Statistical Methods:
The quantitative variables in both groups are expressed as mean±SD and compared using ANOVA and unpaired t-test between groups and paired t-test within each group at various follow-ups. The qualitative variables are expressed as frequencies/percentages and compared using the Chi-square test. A p-value < 0.05 is considered statistically significant. 'R' programming language and/or Statistical Package for Social sciences (SPSS) version 16.0 is used for statistical analysis.

Results:
Baseline heart rate was comparable in all the three groups, which was in group Esmolol 78.88 ± 6.45 beats/min, group Clonidine 77.32± 6.34 beats/min, and in group Lignocaine 77.96 ± 7.17respectively. The p-value all the groups are statistically insignificant. Heart rate was dropped after the study drug and induction and the overall p-value was found to be <0.05 which is statistically significant. After intubation, there is a spike of heart rate (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some times like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean± SD after 4 mins 81.12± 8.28 beats/min almost equal to the basal which is78.88 ± 6.45 beats/min) and the p-value is found to be 0.060 which is statistically insignificant thus there is no significant difference. Whereas in group clonidine the mean and standard deviation of heart rate was found to be equal in 6 min to the basal values the p-value is found to be 0.481 which is statistically insignificant thus there is no significant difference. In group lignocaine, the mean and standard deviation was found to be not equal to basal values even after 8 mins and the p values were found to be <0.001 which is statistically significant.

Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 6 mins after intubation with the p values of 0.110 thus there is no significant difference after 6 mins of intubation. where a comparison between esmolol and lignocaine and group clonidine and lignocaine wasfound to be statistically significant.(Figure 1)

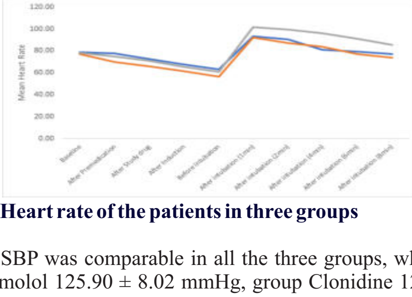

Figure 1.Heart rate of the patients in three groups

Baseline SBP was comparable in all the three groups, which was in group Esmolol 125.90 ± 8.02 mmHg, group Clonidine 124.72 ± 9.3 mmHg, and in group Lignocaine 123.84 ± 7.84 respectively. The overall p-value was calculated and found to be >0.05 which is statistically insignificant. The p-value of base line SBP value comparison between the two groups esmolol and clonidine are 0.249, esmolol and lignocaine are 0.062, and clonidine and lignocaine are 0.229 therefore all the groups are statistically insignificant. Further, in the three groups, the SBP was dropped after study drug and induction and the p-value was found to be <0.05 which is statistically significant. After intubation, there is a spike of SBP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some times like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 128.10 ± 10.13 mmHg almost equal to the basal which is 125.90 ± 8.02 mmHg) and the p-value is found to be 0.071 which is statistically insignificant thus there is no significant difference. In group clonidine, the mean and standard deviation of SBP was found to be equal in 4 min to the basal values (mean± SD after 4 mins 126.68 ± 9.38 mmHg almost equal to basal values which are 124.72 ± 9.3 mmHg) and the p-value is found to be 0.097 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was found to be equal to basal values after 6 mins (mean ± SD after 6 min 123.48 ± 12.51 equal to the basal 123.44 ± 7.84) and the p values was found to be 0.492 which is statistically not significant. Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 4 mins after intubation with the p values of 0.234 thus there is no significant difference after 4 mins of intubation. whereas comparison between esmolol and lignocaine was found to be statistically insignificant at 6 mins after intubation with the p values of 0.414 and group clonidine and lignocaine found to be statistically insignificant at 6 mins after intubation with the p-value of 0.077.(table 1)

Table 1-Systolic blood pressure of the patients in three groups

Blood Pressure (Systolic)	Esmolol			Clonidine			Lignocaine			p value			
	mean	±sd	p value (vs BL)	mean	±sd	p value (vs BL)	mean	±sd	p value (vs BL)	Overall	E vs C	E vs L	C vs L
Baseline	125.90	±8.02	-	124.72	±9.3	-	[illegible]	±7.84	-	[illegible]	0.249	0.062	0.229
After Premedication	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
After Study drug	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
After Induction	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
Before Intubation	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
After intubation (1min)	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
After intubation (2min)	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	<0.001	[illegible]	[illegible]	[illegible]	[illegible]
After intubation (4min)	128.10	±10.13	0.071	126.68	±9.38	0.097	[illegible]	[illegible]	<0.001	[illegible]	0.234	[illegible]	[illegible]
After intubation (6min)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	123.48	±12.51	0.492	[illegible]	[illegible]	0.414	0.077
After Intubation (8min)	117.80	±15.15	<0.001	115.40	±12.16	<0.001	115.12	±15.16	<0.001	0.576	0.158	0.183	0.440

The diastolic blood pressure of the three groups was comparable in all the three groups, which was in group Esmolol 79.96± 6.14 mmHg, group Clonidine 78.14 ±8.29 mmHg, and in group Lignocaine 78.10 ± 7.53 respectively. The overall p-value was calculated and found to be > 0.05 which is statistically insignificant. The p-value of base line DBP value comparison between the two groups esmolol and clonidine are 0.107, esmolol and lignocaine are 0.089, and clonidine and lignocaine are 0.490 therefore all the groups are statistically insignificant. Further, in the three groups, the DBP was dropped after study drug and induction as shown in table 10 and the p-value was found to be <0.05 which is statistically significant. After intubation, there is a spike of DBP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some times like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 80.60 ±7.24 mmHg almost equal to the basal which is 79.96± 6.14 mmHg) and the p-value is found to be 0.258 which is statistically insignificant thus there is no significant difference. In group clonidine, the mean and standard deviation of DBP was found to be equal in 8 min to the basal values (mean ± SD after 8 mins 78.18 ± 9.38 mmHg almost equal to basal values which are 78.14 ±8.29 mmHg) and the p-value is found to be 0.490 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was not found to be equal to basal values even after 8 mins. Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 8 mins after intubation with the p values of 0.369 thus there is no significant difference after 8 mins of intubation. Where a comparison between esmolol and lignocaine and group clonidine and lignocaine was found to be statistically significant. (Table 2)

The mean blood pressure of the three groups (mean ± SD) ,Baseline MAP was comparable in all the three groups, which was in group Esmolol 95.26± 5.69 mmHg, group Clonidine 93.60±5.66 mmHg, and in group Lignocaine 93.22± 5.99 respectively. The overall p-value was calculated and found to be >0.05 which is statistically insignificant. Further, in the three groups, the MAP was dropped after study drug and induction and the p-value was found to be <0.05 which is statistically significant. After intubation, there is a spike of MAP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some time like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 96.46 ± 6.88 mmHg almost equal to the basal which is 95.26± 5.69 mmHg) and the p-value is found to be 0.093 which is statistically insignificant thus there is no significant difference. In group clonidine, the mean and standard deviation of MAP was found to be equal in 6 min to the basal values (mean ± SD after 6 mins 94.38 ± 7.11 mmHg

almost equal to basal values which are 93.60±5.66 mmHg) and the p-value is found to be 0.250 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was not found to be equal to basal values even after 8 mins. Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 6 mins after intubation with the p values of 0.416 thus there is no significant difference after 6 mins of intubation. whereas comparison between esmolol and lignocaine and group clonidine and lignocaine were found to be statistically significant. (Table 3)

Table2-Diastolic blood pressure of the patients in three groups

Blood Pressure (Diastolic)	Esmolol			Clonidine			Lignocaine			p-value			
	mean	±sd	p-value (vs Bsl)	mean	±sd	p-value (vs Bsl)	mean	±sd	p-value (vs Bsl)	Overall	E vs C	E vs L	C vs L
Base line	79.56	±6.14	-	78.14	±6.20	-	78.10	±6.53	-	0.766	0.101	0.080	0.410
After Premedication	78.36	±10.24	<0.001	75.16	±8.89	<0.001	74.38	±8.45	<0.001	0.006	0.018	0.003	0.394
After Study drug	70.62	±7.15	<0.001	71.16	±6.48	<0.001	70.54	±6.15	<0.001	0.410	0.206	0.110	0.542
After Induction	66.32	±8.5	<0.001	64.52	±8.47	<0.001	65.18	±8.44	<0.001	0.479	0.133	0.168	0.489
Before Intubation	62.84	±8.61	<0.001	59.60	±8.37	<0.001	59.36	±8.28	<0.001	0.290	0.113	0.065	0.371
After Intubation (1min)	92.16	±8.24	<0.001	91.42	±9.41	<0.001	96.42	±9.47	<0.001	<0.001	0.766	<0.001	<0.001
After Intubation (2min)	89.60	±8.33	<0.001	88.76	±10.25	<0.001	95.86	±10.12	<0.001	<0.001	0.241	<0.001	<0.001
After Intubation (4min)	80.64	±8.24	0.296	84.68	±8.16	<0.001	91.14	±9.4	<0.001	<0.001	0.113	<0.001	<0.001
After Intubation (6min)	80.08	±10.53	0.451	80.58	±17.70	0.011	89.40	±17	<0.001	<0.001	0.046	<0.001	<0.001
After Intubation (8min)	77.02	±17.11	0.031	78.18	±9.36	0.490	85.10	±17.05	<0.001	<0.001	0.369	<0.001	<0.001

Table 3 - Mean blood pressure of the patients in three groups

Mean Arterial Pressure	Esmolol			Clonidine			Lignocaine			p-value			
	mean	±sd	p-value (vs Bsl)	mean	±sd	p-value (vs Bsl)	mean	±sd	p-value (vs Bsl)	Overall	E vs C	E vs L	C vs L
Baseline	93.26	±5.60		93.60	±5.66		93.22	±6.05		0.175	0.273	0.242	0.979
After Premedication	93.80	±5.38	<0.001	90.26	±6.27	<0.001	85.24	±6.67	<0.001	<0.001	0.002	<0.001	0.223
After Study drug	85.38	±7.44	<0.001	85.26	±6.48	<0.001	84.34	±6.7	<0.001	0.565	0.151	0.210	0.286
After Induction	77.04	±6.28	<0.001	76.22	±5.84	<0.001	76.52	±5.04	<0.001	0.825	0.218	0.273	0.437
Before Intubation	71.62	±6.26	<0.001	71.56	±5.61	<0.001	71.18	±5.67	<0.001	0.706	0.463	0.173	0.571
After intubation (1min)	108.26	±7.52	<0.001	106.72	±4.87	<0.001	112.18	±6.23	<0.001	<0.001	0.206	0.002	<0.001
After intubation (2min)	105.46	±6.24	<0.001	102.48	±5.24	<0.001	108.66	±6.78	<0.001	<0.001	0.242	0.002	<0.001
After intubation (4min)	96.46	±6.58	0.053	96.70	±5.1	<0.001	106.52	±5.2	<0.001	<0.001	0.244	<0.001	<0.001
After intubation (6min)	94.66	±7.05	0.263	94.36	±7.21	0.250	102.72	±6.44	<0.001	<0.001	0.416	<0.001	<0.001
After intubation (8min)	91.04	±6.38	0.061	90.66	±7.86	0.019	95.46	±7.23	0.017	0.002	0.408	0.002	<0.001

Discussion:

During induction, direct laryngoscopy and endotracheal intubation cause sympathoadrenal response and afferent stimulation of the vagus, which might prove harmful to the myocardium and may be fatal to the patient.[6,7] These neuroendocrine responses can cause a variety of complications in patients with cardiac disease due to an imbalance of myocardial oxygen supply and demand like ischemic changes, ventricular arrhythmias, cardiac failure, and raised intracranial pressure. Deep pressure on the base of the tongue due to laryngoscopy and endotracheal intubation is responsible for such response. This is also hazardous in patients with vascular pathologies due to the weakening of the lining of major arteries in particular cerebral and aortic aneurysms. In patients with hydrocephalus or intracranial mass lesions, the increase in blood pressure leads to an increase in CSF pressure which may produce transient impairment of cerebral perfusion leading to cerebral ischemia. In healthy individuals, this momentary reflex is not significant whereas it can be detrimental in patients with hypertension, coronary vascular disease, and cerebrovascular diseases. In such patients, there is a need to blunt this hemodynamic response to endotracheal intubation and laryngoscopy with the help of prophylaxis in the form of antihypertensive agents, beta-blockers, narcotics, and other drugs. These stimuli are responsible for activating suprasegmental and hypothalamic sympathetic centres to cause a peripheral sympathoadrenal response which releases catecholamines.[70]To circumvent these responses, our study was undertaken. For safe conduct of anaesthesia, the pressor response to laryngoscopy and endotracheal intubation needs to be blunted so in our study we have compared the three drugs clonidine, esmolol, and lignocaine as an adjuvant to fentanyl to attenuate the pressor response to laryngoscopy during endotracheal intubation. Heart rate variation decreases with increasing age in young patients and extreme age. [8,9] Keeping it in view we have considered patients between 18-65 years in our study. Various drug regimens and techniques such as lignocaine, opioids, nitroglycerine, calcium channel blockers such as diltiazem, and beta-blockers such as esmolol have been tried for obtunding the stress response.[10,11] In our study we have compared the three drugs clonidine, esmolol, and lignocaine as an adjuvant to fentanyl. Esmolol is a highly cardio selective agent, analogous to metoprolol, and so is unlikely to induce bronchospasm. It undergoes rapid esterase-mediated metabolism, characterized by an elimination half-life of 9.2 min (ultrashort duration of action (9 min)[12]) and total body clearance of 285 ml min"1, culminating in a rapid offset of action when the infusion is discontinued [13]. In esmolol, significant drug interactions have not been reported yet [14] and the only adverse effects reported are hypotension and thrombophlebitis at the site of injection. The latter sequel can be avoided by careful dilution of the agent (5 mg/ml) and the judicious use of doses. ß-blocker esmolol possesses several properties which make it a valuable agent to obtund the cardiovascular response. Korpinen *et al*. (1998) reported that the administration of esmolol bolus 2 mg kg^{-1} IV 2 min before laryngoscopy and intubation suppressed the increase in the heart rate rather than arterial blood pressures.[15]

Other studies concluded that esmolol 1.5 mg/kg is effective in attenuating hemodynamic response to laryngoscopy and intubation, Bostana and Eroglu (2012)78 reported that IV esmolol in the dose of 1 mg kg^{-1} before intubation was effective in suppressing the heart rate and arterial blood pressure. [12,16,17] In our study we are considering iv esmolol in the dose of 1.5mg/kg adjuvant to fentanyl Alpha 2 agonists clonidine, works by stimulating α2 adrenergic inhibitory neurons in the medullary vasomotor center. As a result, there is a decrease in sympathetic nervous system outflow from the central nervous system to peripheral tissues.[18] Activation of central α -2 adrenergic receptors in the medullary vasomotor center inhibits the release of norepinephrine from the adrenergic neurons which reduces the sympathetic outflow from the central nervous system. Further, there is reduced discharge from the postganglionic fibers of cardiac nerves results in an increase in parasympathetic tone. This decreases blood pressure, heart rate, cardiac output, and peripheral venous resistance. Clonidine is mainly used as an antihypertensive agent but has been found to have beneficial effects in attenuating hemodynamic responses to laryngoscopy and intubation, especially in i.v. route rather than the oral route. intravenous clonidine 2 μg/kg 5 minutes before the laryngoscopy to attenuate the sympathetic response to the laryngoscopy and the intubation.[18] In our study, we have taken the dose of clonidine as 1.5 μg/kg adjuvant to fentanyl (2mcg/kg).

The effects of clonidine on HR and BP have been studied and found that the reduction in the pulse rate after the clonidine administration is due to a combination of reduction in the sympathetic outflow, the simultaneous increase of the parasympathetic tone of central origin, and the influence of clonidine on the neurons which receive the baroreceptor afferents. Clonidine alters HR mainly through its direct central action on the baroreceptor pathways.[19] In the clonidine group, a rise in HR was observed in our study after intubation which reached baseline values by 6 min (mean ± SD after 6 mins 77.38 ± 5.44 beats/min almost equal to basal values which are 77.32 ± 6.34 beats/min) where as in a study HR in clonidine group reached equal to basal in 10 mins.[20] Lignocaine is a synthetic amide local anaesthetic. Lignocaine holds the tendency to blocks the fast sodium channels in the cell membranes of myocardial cells which reduces the rate of rising of the action potential in the His Purkinje system and the ventricular musculature. The duration of the action potential and effective refractory period are reduced. The sinoatrial node and atrioventricular node are not affected by therapeutic concentrations of lignocaine. Possible mechanisms by which it attenuates the hemodynamic response to laryngoscopy and intubation include direct myocardial depressant effect, peripheral vasodilatation, and inhibition of synaptic transmission. Several preparations are available now. Various researchers have conducted studies to see the effect of various forms of lignocaine on hemodynamic response to laryngoscopy and intubation with varied results. In 1977 Stoelting, R *et al* [21]. concluded that lignocaine1.5 mg/kg intravenously can attenuate the pressor response effectively[21,22,23,24]. But the group of patients who were treated only with lignocaine, their sympathetic responses did not come down to baseline at 5 minutes after laryngoscopy and endotracheal intubation.

In our study in the Esmolol group, a rise in HR occurred during intubation which reach baseline values (mean ± SD is 78.88 ± 6.45 beats/min) after 4 min (mean ± SD is 81.12± 8.28 beats/min). This finding corroborates with the findings of Feng CK *et al.*[25] and Agrawal P *et al* [26]concluded that the esmolol group when compared with its baseline values, showed a significant rise in heart rate only at 1 minute and 2 minutes after intubation and reached equal to baseline in 4 min. In group lignocaine, the mean and standard deviation was found to be not equal to basal values even after 8 mins as was mentioned by Mollick*et al.*[19]in his study. In a study byRoutray SS *et al.*[19], Fentanyl and fentanyl plus lidocaine are equally effective in decreasing the hemodynamic stress response to tracheal intubation, but neither fentanyl nor fentanyl plus lidocaine could inhibit all hemodynamic responses, furthermore, fentanyl plus lidocaine was not more effective than fentanyl alone. In our study lignocaine, adjuvant to fentanyl was not able to control heart rate response even 8 mins after intubation. Sympathetic response to laryngoscopy and intubation was seen at 1min following intubation in our study in all three groups. As per our statistical observation with ANOVA (analysis of variance) test, the

sympathetic response is suppressed in all three groups when considered independently which is statistically significant ($p<0.001$). Categorically, clinical parameter (HR) when compared with Chi-square or Fisher exact test, between Esmolol-Clonidine and Esmolol-Lignocaine, post-intubation the hemodynamic response was suppressed, which was statistically significant $p<0.001$. The p-value of base line heart rate value comparison between the two groups esmolol and clonidine is 0.113, esmolol and lignocaine are 0.251, and clonidine and lignocaine are 0.319; therefore, all the groups are statistically insignificant. Among the two groups comparison, esmolol and clonidine were statistically insignificant at 6 mins after intubation with the p values of 0.110;thus there is no significant difference after 6 mins of intubation. whereas comparison between esmolol and lignocaine and group clonidine and lignocaine wasfound to be statistically significant. and Kumar *et al*[17], showed that esmolol in a dose of 2 mg/kg, blunts the SBP response postintubation. In our study baseline SBP was comparable in all the three groups, which was in group Esmolol 125.90 ± 8.02 mmHg, group Clonidine 124.72 ± 9.3 mmHg and in group Lignocaine 123.84 ± 7.84 respectively. The overall p-value was calculated and found to be >0.05 which is statistically insignificant. The p-value of base line SBP value comparison between the two groups esmolol and clonidine are 0.249, esmolol and lignocaine are 0.062, and clonidine and lignocaine are 0.229 therefore all the groups are statistically insignificant. Further, in the three groups, the SBP was dropped after study drug and induction and the p-value was found to be <0.05 which is statistically significant. After intubation, there is a spike of SBP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some times like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 128.10 ± 10.13 mmHg almost equal to the basal which is 125.90 ± 8.02 mmHg) and the p-value is found to be 0.071 which is statistically insignificant thus there is no significant difference. In group clonidine, the mean and standard deviation of SBP was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 126.68 ± 9.38 mmHg almost equal to basal values which are 124.72 ± 9.3 mmHg) and the p-value is found to be 0.097 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was found to be equal to basal values after 6 mins (mean ± SD after 6 min 123.48 ± 12.51 equal to the basal 123.44 ± 7.84) and the p values was found to be 0.492 which is statistically not significant.

Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 4 mins after intubation with the p values of 0.234 thus there is no significant difference after 4 mins of intubation. whereas comparison between esmolol and lignocaine was found to be statistically insignificant at 6 mins after intubation with the p values of 0.414 and group clonidine and lignocaine found to be statistically insignificant at 6 mins after intubation with the p-value of 0.077. The findings are very much similar to the observations of other studies. Parvez G *et al* [28]compared the rate pressure product between esmolol and diltiazem groups and found that there was a significant difference between them at different time intervals. Esmolol group showed lesser values at all time intervals. It was found in the present study that esmolol was significantly better than other drugs for attenuating the rate pressure product at all time intervals. Talwar (2018) *et al.*[29]study reported that HR was significantly less in the combination (esmolol+Dilzem) and esmolol groups as compared to the control till 5 min after laryngoscopy and tracheal intubation. As compared with the control, all the other groups were associated with a fall in SBP after the test dose, and this lasted for 5 min ($P < 0.001$) after laryngoscopy in the esmolol and combination groups and for 1 min ($P < 0.001$) in the diltiazem group. All groups were associated with a significant rise in DBP and MAP for 1–2 min after laryngoscopy and tracheal intubation ($P < 0.001$), except the combination group in which no change was noted. DBP and MAP were significantly less in the combination group as compared to the control, from 1 min after giving the test dose till 5 min ($P < 0.001$) after laryngoscopy and tracheal intubation whereas in our study after intubation there is a spike of DBP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some times like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins mmHg almost equal to the basal which is 80.60 ±7.24 mmHg) and the p-value is found to be 0.258 which is statistically insignificant thus there is no significant difference. In group clonidine the mean and standard deviation of DBP was found to be equal in 8 min to the basal values (mean ± SD after 8 mins 78.18 ± 9.38 mmHg almost equal to basal values which are 78.14 ±8.29 mmHg) and the p-value is found to be 0.490 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was not found to be equal to basal values even after 8 mins. Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 8 mins after intubation with the p values of 0.369 thus there is no significant difference after 8 mins of intubation. whereas the comparison between esmolol and lignocaine and group clonidine and lignocaine wasfound to be statistically significant. Singh *et al*.[27] showed that esmolol 1.4 mg/kg was significantly more effective than lignocaine 1.5 mg/kg in minimizing the increase in MAP.[3] Helfman *et al.* reported significant attenuation of heart rate, SBP and MAP in bolus doses of esmolol 200 mg.[28] mulimani et al in his study concluded that the mean pulse rate, mean of MAP, and mean of RPP (Rate pressure product) at intubation and at 1, 2, 3, and 5 min after intubation in lignocaine group showed a significant rise in these values but in esmolol group it remained nearer to or less than baseline values where as in our study After intubation there is a spike of MAP (mean ± SD) noted in all three groups from basal (mean ± SD) which get settled after some time like in group esmolol the mean and standard deviation was found to be equal in 4 min to the basal values (mean ± SD after 4 mins 96.46 ± 6.88 mmHg almost equal to the basal which is 95.26± 5.69 mmHg) and the p value is found to be 0.093 which is statistically insignificant thus there is no significant difference. In group clonidine, the mean and standard deviation of MAP was found to be equal in 6 min to the basal values (mean ± SD after 6 mins 94.38 ± 7.11 mmHg almost equal to basal values which are 93.60±5.66 mmHg) and the p-value is found to be 0.250 which is statistically insignificant thus there is no significant difference. Whereas In group lignocaine the mean and standard deviation was not found to be equal to basal values even after 8 mins which coincide with other studies. Among the two groups comparison, esmolol and clonidine were found to be statistically insignificant at 6 mins after intubation with the p values of 0.416 thus there is no significant difference after 6 mins of intubation. whereas comparison between esmolol and lignocaine and group clonidine and lignocaine wasfound to be statistically significant. Bakiye Ugur *et al* (2007)[30, 31] studied the Effects of esmolol, lidocaine, and fentanyl on hemodynamic responses to endotracheal intubation and It can be concluded that administration of esmolol 1.5 mg/kg 2 minutes before intubation prevents tachycardia and an increase in RPP caused by laryngoscopy and tracheal intubation, and can be beneficial when administered before laryngoscopy and tracheal intubation in patients with tachycardia in our study we have taken a same intravenous dose of esmolol 1,5mg/kg but we have administered the dose 3 minutes before intubation and the result coincides with the above study. Fentanyl is a potent, synthetic narcotic analgesic. It has a rapid onset and short duration of action and is extremely lipid-soluble. Holds a low molecular weight and is a synthetic opioid agonist who is popularly used as an intravenous analgesic supplement, the component of inhalation anaesthesia, balanced anaesthesia, and neurolept analgesia, and also as a sole anaesthetic. It is 75 to 125 times more potent than morphine as an analgesic [30]. After administration, the onset of action starts in 1-2 minutes, and the duration is 1 hour. Many studies have proved that it is ideal for control of the short-lived hemodynamic squeal, associated with laryngoscopy and intubation. In our study, we have considered the fentanyl adjuvant to all three drugs for suppression of hemodynamic response to laryngoscopy and endotracheal intubation. Fentanyl is taken in the dose of 2mcg/kg and administered 3 mins before laryngoscopy and endotracheal intubation in all three groups.

Sathappan Karuppiah *et al* (2021) studied the Attenuation of hemodynamic response to laryngoscopy and intubation using intravenous fentanyl and esmolol. They studied Ninety patients undergoing surgical procedures, they were allocated into three groups viz., Group I (control): Identical volume of normal saline intravenously (IV) 3 min before induction; Group II (fentanyl): Injection fentanyl 2 mcg/kg IV 3 min before induction; Group III (esmolol): Injection esmolol 0.2 mg/kg i.v 3 min before induction. The heart rate and arterial blood pressure changes were monitored: Before intubation, at intubation, and after intubation at different time intervals. In their studies Changes in the systolic blood pressure (SBP) were found to be minimum with fentanyl and esmolol groups when compared to the control group ($P < 0.001$). The diastolic blood pressure and mean arterial pressure changes were significant between fentanyl

and esmolol groups with the control but not between esmolol and fentanyl. Group II showed better control of heart rate during laryngoscopy and intubation at the first min after intubation compared to other groups ($P < 0.05$). They concluded that Fentanyl 2 µg/kg bolus or esmolol 0.2 mg/kg bolus 3 min before induction significantly attenuates the hemodynamic response to laryngoscopy and intubation better than the control group whereas in our study we have taken fentanyl as an adjuvant in all our groups to the study drug to achieve better result [33]. Blood pressure response, comparison between Esmolol-Lignocaine and Clonidine-Lignocaine, fall in blood pressure was statistically significant ($p<0.001$) between the groups. The inference is that in-group Lignocaine post-intubation response suppression was statistically significant in maximum scenarios. Whereas in comparison between Esmolol-Clonidine, fall in BP (SBP, DBP, and MAP) was statistically insignificant in some scenarios like in SBP they were insignificant at 4 mins, in DBP were statistically insignificant at 8 mins and in MAP statistically insignificant at 6 mins. There were many limitations in our study. During the study,we were unable to assess the plasma level of catecholamines. In our study, we had taken only the changes in normotensive patients and ASA I and II, not comorbid patients. Hence, further studies are required to know the effective, attenuation of hemodynamic response to laryngoscopy and endotracheal intubation with the help of the drugs to prevent pressor response in high-risk patients.

Conclusion:

From our present study, it is concluded that drug esmolol intravenously is more effective than drug clonidine and drug lignocaine as an adjuvant to fentanyl in attenuating the hemodynamic response to laryngoscopy and endotracheal intubation. Esmolol and clonidine as an adjuvant to fentanyl has good control on HR, SBP, DBP and MBP among all three drugs but esmolol with fentanyl has better control on HR than clonidine with fentanyl. Lignocaine as an adjuvant didn't show significant effect on neither HR nor DBP and MBP but it showed good result only on SBP. Considering all parameters, we conclude that esmolol with fentanyl showed better response on all parameters.

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