International Journal of Biomedical Research
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: 10.7439/ijbr
CODEN: IJBRFA

Original Research Article

A prospective randomized double blind study to compare the efficacy of oral Clonidine to intravenous Lignocaine for attenuation of haemodynamic response to laryngoscopy and tracheal intubation

Sweetline Subha M, Sasidharan Nair M, M. Paul Wilson, Ashabi M and Salini R Varma

Department of Anaesthesia, SMCSI Medical College, Karakonam – 695504 India

***Correspondence Info:**
Dr. M. Paul Wilson
Professor,
Department of Anaesthesia,
SMCSI Medical College, Karakonam – 695504
E-mail: paulwilson555@gmail.com

Abstract

A randomized double blinded controlled study was done with oral Clonidine and intravenous Lignocaine. The aim of the study was to compare the laryngoscopy and intubation responses after the administration of the study drug and the control drug. In this study conducted in Regional Cancer centre, Trivandrum we selected 38 patients each in Group A who received oral Clonidine and Group B who received intravenous Lignocaine. The haemodynamic responses in both groups were compared. We concluded that oral Clonidine has better control over haemodynamic responses to laryngoscopy and intubation when compared to intravenous Lignocaine.

Keywords: Tracheal intubation, laryngoscopy, Clonidine, Lignocaine, haemodynamic responses.

1. Introduction

Current general anaesthesia involves endotracheal intubation with direct laryngoscopy after induction with intravenous anesthetic agent and a muscle relaxant. Tachycardia and hypertension along with increase in cardiac output and central venous pressure are well documented complications of laryngoscopy and tracheal intubation in anaesthetic practice. These reflex responses to airway stimulation, first enunciated by King *et al* in 1951 are universal accompaniments of light general anaesthesia[1].

The increase in heart rate and arterial blood pressure is associated with increase in plasma catecholamine concentration and is mediated by increased sympathetic nervous system activity provoked by stimulation of epipharynx and laryngopharynx. This response may be exaggerated in patients with treated or untreated essential hypertension who have a greater incidence of coexisting coronary artery or cerebrovascular disease.

Although these haemodynamic responses are transient and probably of little consequence in healthy individuals, they may be deleterious in patients with cardiovascular diseases like hypertensives with impending cardiac failure, ischaemic heart disease or neurovascular disease and in those with raised intracranial tension.

Many methods of attenuating these responses have emerged. It could be achieved by deepening the level of anaesthesia with inhalational agents or by using local anaesthetics (topical or intravenous Lignocaine) or narcotics like fentanyl and alfentanyl. Agents to control tachycardia like betablockers, vasodilators like sodium nitroprusside and antihypertensive agents like Clonidine are also employed [2].

In the present study, an assessment of the efficacy of oral Clonidine and intravenous Lignocaine in attenuating these haemodynamic responses to laryngoscopy and endotracheal intubation was studied.

Clonidine has the added advantage of reduction in the requirement of anaesthetic agents during maintenance of anaesthesia as well as contribute to analgesia in the per operative and post operative period [3-6]. However the role of oral Clonidine in attenuating the pressor response has not been widely studied in our country.

Oral Clonidine is readily available, cheap and easy to administer. If it is effective to attenuate pressor response, it could be easily incorporated into our premedication regime.

2. Materials and Methods

It is planned to conduct a randomised double blinded trial involving 76 patients belonging to ASA grade I and II undergoing major elective surgeries under general anaesthesia. Patients were allocated to group A [receiving oral Clonidine 200mcg and 5ml intravenous normal saline] and group B [multivitamin 1 tab and 1.5mg/kg intravenous Lignocaine made into 5ml] using computer generated randomization chart. This study was conducted at the Department of Anaesthesiology, Regional Cancer Centre, Thiruvananthapuram.

2.1 Selection of patients

Assuming the power of study as 80% and the level of significance as 5% anticipated benefit rate of oral Clonidine to be 60%{20% higher than control}, sample size of 38 in each arm was decided. 76 cases of ASA I & II between the age group of 20 & 60 years coming for mastectomy were included in the study. The following patients were excluded from the study.

1. Patients below 20 yrs and above 60 yrs
2. ASA grade III & IV
3. Mallampatti III & IV
4. Anticipated difficult intubation
5. Patients with history of renal insufficiency
6. Patients with history of coronary artery disease
7. Patients with history of hypertension and diabetes mellitus on medication
8. Patients weighing less than 40 kgs and more than 70 kgs to standardize the dose of Clonidine and Lignocaine.

2.2 Methodology

Approval from the institutional review board and ethical committee of the institution was obtained prior to starting the study. All the patients who met inclusion criteria were explained about the study in detail in their own language and informed consent was obtained.

All the patients were premedicated with tab diazepam 5mg, tab metaclopromide 10mg and tab ranitidine 150mg one hour before the induction. All the patients in the Clonidine group were administered with oral Clonidine 200 microgram and Lignocaine group were given a multivitamin tablet one hour before the induction of anesthesia. All the patients were premedicated with Inj Morphine 0.1mg/kg, Promethazine 12.5mg and inj Glycopyrrolate 0.2mg intramuscularly 45 minutes prior to the anticipated time of induction.

Intravenous access was obtained for all patients using 18 gauge cannula on the forearm and 0.9 % normal saline was started. Multi parameter monitor would be connected to record the ECG, heart rate, noninvasive blood pressure, SpO_2 and $ETCO_2$. Induction technique would be similar for all the patients. The principal investigator who is blind to which category the patient belongs to, would preoxygenate and the induction agents will be administered. Patients in group A would receive 5 ml of intravenous normal saline and group B would receive 1.5mg/kg of intravenous Lignocaine made into 5 ml followed by Thiopentone sodium 5mg/kg over 30 seconds. Then Succinylcholine 1.5mg/kg intravenously would be given by qualified assistant for both the groups.

Artificial ventilation will be commenced with 100% oxygen through face mask of appropriate size using Bain's circuit during the period of Succinylcholine apnea. Sixty seconds later a gentle direct laryngoscopy will be performed with a Macintosh curved blade laryngoscope and intubated with appropriate sized cuffed oral endotracheal tube. All the intubations were done by the same person. The patients were ventilated manually with Nitrous Oxide and Oxygen in a ratio of 66:34 and Halothane 0.5%. Pulse rate and blood pressure were noted before induction, just immediately after intubation and subsequently at intervals of 3, 5 and 7 minutes. During these 7 minutes patients were not manipulated or subjected to any surgical stimulation.

Muscle relaxation was maintained with Vecuronium. Anaesthesia was maintained with Oxygen, Nitrous oxide, Halothane and Intermittent Positive Pressure Ventilation. Fentanyl was used as analgesic as required. Pulse rate and blood pressure were recorded every 10 minutes. At the end of surgery the patient was reversed with 0.05 mg/kg of Neostigmine and 0.01mg/kg of Glycopyrrolate. Adequate ventilation was ensured and the patient would be shifted to the recovery room after extubation.

2.3 Statistical Methods

Data were collected using predesigned proforma. Student t test was used to compare the mean between the two groups. P value of less than 0.05 was considered statistically significant.

3. Results:

3.1 Age

Table 1: Distribution according to age

Group	Age in years		Total
	Below 40 years	40 & above	
Clonidine	15 (39.5%)	23 (60.5%)	38(100.0%)
Lignocaine	12(31.6%)	26(68.4%)	38(100.0%)
Total	27(35.5%)	49(64.5%)	38(100.0%)
Chi square =0.571;p value = 0.316 (N.S)			

From Table 1 it can be seen that 39.5% of the patients in the Clonidine group, 31.6% of the patients in Lignocaine group were in below 40 years of age group. Though numerically a lower percentage of patients were in below 40 years in Lignocaine group compared to Clonidine group the difference in percentage was not statistically significant. Chi square =0.571; p value = 0.316 (N.S). So it is inferred that both the groups were comparable in terms of age.

3.2 Weight

Table 2: Distribution according to Weight

Distribution according to weight				Total
Drug groups		<50 Kg	≥ 50kg	
Clonidine	Count	25	13	38
	% within Drug groups	65.8%	34.2%	100.0%
Lignocaine	Count	28	10	38
	% within Drug groups	73.7%	26.3%	100.0%
Total	Count	53	23	76
	% within Drug groups	69.7%	30.3%	100.0%
Chi square =0.561; p value = 0.309 (N.S)				

While considering the distribution according to weight, no marked significant difference noted between the two groups. Under 50 Kg weight category Clonidine group have 65.8% and lignocaine group have 73.7%. Likewise in ≥ 50 Kg category Clonidine group have 34.2% and lignocaine group have 26.3%. Since no statistically significant difference is noted, both the groups are found to be identical with respect to weight.

3.3. Pulse Rate

Table 3: Mean, SD, and level of significance of pulse rate in Clonidine group and Lignocaine group according to time of assessment

	Drug groups	Mean	Std. Deviation	p value
Base Line (Pulse rate)	Clonidine	83.5789	4.4274	0.595
	Lignocaine	83.0526	4.1522	
After Premedication	Clonidine	77.6579	5.3184	0
	Lignocaine	82.2895	3.9994	
Before laryngoscopy	Clonidine	75.5263	6.3957	0
	Lignocaine	83.3421	5.6534	
After laryngoscopy	Clonidine	81.0263	7.8860	0
	Lignocaine	94.7105	7.8599	
After 2 mts	Clonidine	80.1053	7.6398	0
	Lignocaine	93.5263	7.5004	
After 3 mts	Clonidine	78.5263	7.6608	0
	Lignocaine	90.8947	7.1350	
After 5 mts	Clonidine	77.5789	7.2880	0
	Lignocaine	88.0789	5.3189	
After 7 mts	Clonidine	76.6316	7.0994	0
	Lignocaine	85.7895	4.5747	

The mean baseline pulse rate in the Clonidine group was 83.57 while in Lignocaine group it was 83.05. The p value was 0.595 which was not statistically significant. The mean pulse rate in Clonidine group (75.53) showed significant difference from Lignocaine group (83.34) before laryngoscopy. The p value was 0.000 which was statistically significant. The difference in the mean pulse rate between the two groups was found to be statistically significant after laryngoscopy (Clonidine - 81.03, Lignocaine - 94.71), 2 minutes (80.10,93.53), 3minutes (78.53,90.89), 5 minutes (77.58,88.08) and 7 minutes (76.63,85.79) after laryngoscopy with p values of 0.000.

3.4. Systolic Blood Pressure

Table 4: Mean, SD, and level of significance of Systolic blood pressure in Clonidine group and Lignocaine group according to time of assessment

	Drug groups	Mean	Std. Deviation	p value
Base Line (Systolic BP)	Clonidine	110.3947	7.6319	0.214
	Lignocaine	115.0000	9.2269	
After Premedication	Clonidine	107.1842	5.8948	0
	Lignocaine	115.0263	8.3746	
Before laryngoscopy	Clonidine	105.8421	4.5591	0.018
	Lignocaine	109.5789	8.4041	
After laryngoscopy	Clonidine	118.1053	6.4338	0.001
	Lignocaine	124.5263	9.5655	
After 2 mts	Clonidine	116.5263	6.2157	0.001
	Lignocaine	123.1053	9.8139	
After 3 mts	Clonidine	114.7632	5.9340	0.008
	Lignocaine	119.5000	8.9827	
After 5 mts	Clonidine	112.7895	5.5173	0.031
	Lignocaine	116.3421	8.3059	
After 7 mts	Clonidine	110.9737	5.0107	0.112
	Lignocaine	113.4211	7.9207	

The systolic blood pressure was proved to be almost identical in both the groups before induction with p value of 0.214. The systolic blood pressure before, immediately after, and 2, 3, 5 minutes after laryngoscopy showed significant difference between two groups with p values of 0.018, 0.001, 0.001, 0.008 and 0.031 respectively.

3.5 Diastolic Blood Pressure

Table 5: Mean, SD and level of significance of Diastolic BP in Clonidine group and Lignocaine group according to time of assessment

	Drug groups	Mean	Std. Deviation	p value
Base Line (Diastolic BP)	Clonidine	79.5526	5.4708	0.119
	Lignocaine	77.6053	5.3045	
After Premedication	Clonidine	77.7632	5.2062	0.730
	Lignocaine	78.1842	5.4020	
Before laryngoscopy	Clonidine	77.6842	6.3079	0.403
	Lignocaine	76.4737	6.2460	
After laryngoscopy	Clonidine	86.7368	4.9576	0.016
	Lignocaine	83.2895	7.0745	
After 2 mts	Clonidine	85.5526	4.7913	0.008
	Lignocaine	82.2368	5.7864	
After 3 mts	Clonidine	84.0526	4.5556	0.003
	Lignocaine	80.3421	5.8784	
After 5 mts	Clonidine	81.8421	4.5591	0.041
	Lignocaine	79.4211	5.5343	
After 7 mts	Clonidine	80.6053	4.7222	0.090
	Lignocaine	78.6316	5.2783	

The diastolic blood pressure was proved to be almost identical in both the groups before induction with p value of 0.119. The diastolic blood pressure immediately after, and 2, 3, 5 minutes after laryngoscopy showed significant difference between two groups with p values of 0.016, 0.008, 0.003, 0.041 respectively.

3.6 Mean Arterial Pressure (MAP)

Table 6: Mean, SD, and level of significance of MAP in Clonidine group and Lignocaine group according to time of assessment

	Drug groups	Mean	Std. Deviation	p value
Base Line (Mean arterial pressure)	Clonidine	90.0789	5.2986	0.476
	Lignocaine	90.0000	5.4871	
After Premedication	Clonidine	87.5789	4.5597	0.015
	Lignocaine	90.4474	5.3962	
Before laryngoscopy	Clonidine	87.1842	4.9585	0.983
	Lignocaine	87.2105	5.9054	
After laryngoscopy	Clonidine	97.1842	4.5074	0.930
	Lignocaine	97.2895	5.8859	
After 2 mts	Clonidine	95.7895	4.4731	0.772
	Lignocaine	95.4474	5.6983	
After 3 mts	Clonidine	94.2105	4.1795	0.470
	Lignocaine	93.3947	5.5192	
After 5 mts	Clonidine	92.1316	4.2053	0.693
	Lignocaine	91.7105	5.0291	
After 7 mts	Clonidine	90.8158	4.0925	0.575
	Lignocaine	90.2368	4.8348	

The mean arterial blood pressure did not show any significant difference between two groups except after premedication with p value of 0.015.

3.7. Rate Pressure Product (RPP)

Table 7: Mean, SD and level of significance of RPP in Clonidine group and Lignocaine group according to time of assessment

	Drug groups	Mean	Std. Deviation	p value
Base Line (Rate pressure product)	Clonidine	9230.4474	844.0219	0.275
	Lignocaine	9542.7895	817.5689	
After Premedication	Clonidine	8328.1842	786.3023	0
	Lignocaine	9456.9737	727.1947	
Before laryngoscopy	Clonidine	7998.4211	775.0972	0
	Lignocaine	9135.5789	968.7319	
After laryngoscopy	Clonidine	9578.4211	1147.6165	0
	Lignocaine	11804.0000	1410.8616	
After 2 mts	Clonidine	9343.3684	1099.3801	0
	Lignocaine	11516.4737	1318.2604	
After 3 mts	Clonidine	9019.1579	1058.4447	0
	Lignocaine	10859.4211	1137.4319	
After 5 mts	Clonidine	8756.2368	988.2085	0
	Lignocaine	10243.1842	898.0085	
After 7 mts	Clonidine	8506.6053	898.5405	0
	Lignocaine	9724.5263	774.1495	

The rate pressure product was proved to be almost identical in both the groups before induction with p value of 0.275. The rate pressure product before, immediately after, and 2,3,5,7 minutes after laryngoscopy showed significant difference between two groups with p values of 0.

4. Discussion

4.1 Stress Response and Anaesthesia[10]

4.1.1 Stress Response:

The body reacts to external stimuli ranging from minor to massive insults both locally and generally. The general response is in the form of widespread endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of response is highly dependent on the severity, intensity and the duration of stimulus. Such a reflex to insults is affected through the autonomic nervous system, triggered by a complex interplay of substances in the hypothalamic-pituitary axis (the classical neuro endocrine hormone system).

The net effect of stress response "The neuroendocrinal outflow"

Cardiovascular changes:--Rise in cardiac output, heart rate, blood pressure, increased myocardial contractility, increased oxygen demand.

Blood volume distribution:-- Peripheral and splanchnic vasoconstriction, Coronary and Cerebral vasodilatation.

Respiratory Changes:-- Increased respiratory rate.

Fluid and electrolyte changes:-- Sodium and water retention.

Coagulation:-- Hypercoagulability and fibrinolysis.

Immunosupression:-- Wound infections.

Metabolic changes:-- Substrate mobilization- hyperglycemia.

Urinary changes:-- Reduced urinary output.

4.1.2 Components of stress response

The stress response is made up of two major components, both mediated via the hypothalamus. They are the adrenergic response and the pituitary –hormonal response.

4.1.3 Stimulus for stress response

One of the afferent stimuli for the stress response is the peripheral noxious stimuli. Certain drugs or procedures, light planes of anaesthesia and maximum stimulation (laryngoscopy/ intubation, skin incision, tissue handling) show exaggerated responses.

4.1.4 Regulation of stress response

The hypothalamus and the endocrine system are intimately involved in regulating the body's stress response.

1. The hypothalamus secretes corticotrophin releasing factor which stimulates the anterior pituitary gland to release ACTH and several endogenous opioid polypeptides.
2. It stimulates the sympathetic nervous system and adrenal medulla, simultaneously inhibiting parasympathetic nervous system.
3. It causes release of ADH and Vasopressin from the posterior pituitary.

The stress hormones:- Autocrines - catecholamines, insulin, glucagons; Endocrines - Hormones under hypothalamo-pituitary control like cortisol, thyroxin, angiotensin vasopressin, growth hormone; Cytokines.

The central key is the excitation of the hypothalamus during stress resulting in the secretion of ACTH which in turn initiates sudden increase in cortisol level and the metabolic effects of cortisol are directed to overcome the stressful state.

During the mechanical stimulation of upper respiratory tract viz nose, epipharynx, laryngopharynx, the afferents are carried by glossopharyngeal nerve and from tracheobronchial tree via the vagus nerve which enhance the activities of the cervical sympathetic afferent fibers resulting in transient rise in heart rate and blood pressure.

The use of Clonidine premedication has several advantages as per previous studies. Review of literature showed several studies related to use of Clonidine for the attenuation of pressor response to Laryngoscopy and Tracheal intubation. Some of the relevant studies are cited below.

Laryngoscopy and tracheal intubation after induction of anaesthesia are frequently associated with transient hypertension, tachycardia and arrhythmias. This pressor response has been recognized since 1951. King (1951) and colleagues first described the reflex circulatory responses to airway stimulation. Although these responses are transient, they may be deleterious in some patients [1].

Derbyshire *et al* (1983) demonstrated a good correlation between the pressor response and changes in plasma catecholamine concentrations [2].

Tomori and Widdicombe (1969) observed that mechanical stimulation of four areas of upper respiratory tract – the nose, epipharynx, laryngopharynx and the tracheobronchial tree induced reflex cardiovascular response. They have shown that in a paralysed cat, nervous activity in cervical sympathetic efferent fibres was significantly increased by stimulation of epipharynx and laryngopharynx only, which also caused the greatest increase in mean arterial pressure. Stimulation of the tracheobronchial tree did not produce a significant increase in the activity of these fibres and caused only a small increase in arterial pressure [11].

Shribman and colleagues (1987) have shown that laryngoscopy alone generates the same pressor response and sympathoadrenal response in terms of circulating catecholamine concentration. This suggests that the major cause of sympathoadrenal response to tracheal intubation arises from stimulation of supraglottic region by tissue tension induced by laryngoscopy and that intubation and inflation of the cuff in the infraglottic region contributes very little additional stimulation. Intubation however was associated with significant increase in heart rate which did not occur in laryngoscopy alone group.[12] Wycoff compared laryngoscopy and tracheal intubation under general anaesthesia with the same procedure under surface anaesthesia produced by cricothyroid block. The block produced smaller changes both in blood pressure and heart rate [13].

Takeshema compared the effects of laryngoscopy with different laryngoscopic blades and concluded that the Macintosh blade which compressed the soft tissues of the anterior epipharynx produced a significantly greater hypertensive response than the straight bladed Wis-Foregger laryngoscope [14].

In short, whatever the technique is used or whichever laryngoscope is used, there is a significant increase in blood pressure and heart rate following laryngoscopy and intubation. The stress response produced is probably of no consequence in healthy individuals. It is potentially hazardous in those with hypertension, coronary insufficiency or cerebrovascular disease.

Hypertensive patients have an exaggerated vasopressive response to many forms of stress both in the conscious and the anaesthetized state. Patients on antihypertensive drugs are equally prone to develop cardiovascular disturbances in response to endotracheal intubation and the hypertensive reaction in these subjects is frequently accompanied by dysrhythmias.

From clinical observation in hypertensive patients, Dingle has found a rise in systolic blood pressure of more than 100 mm of Hg following tracheal intubation. A rise in pressure of this order is potentially dangerous and may lead to left ventricular failure and cerebral haemorrhage[15].

Forbes and Dally have observed that acute hypertension during induction of anaesthesia and endotracheal intubation could cause left ventricular failure, mycocardial ischaemia and cerebral haemorrhage[16].

Fox and Sklar showed that increase in blood pressure and heart rate though transitory was variable and unpredictable. They found that hypertensive patients are more prone to have significant increase in blood pressure whether they are treated or not. Two cases have been reported in which complications followed hypertensive episodes directly related to laryngoscopy and endotracheal intubation [17].

Takeshema, Forbes and Dally have established that the mean increase in arterial pressure was of the order of 20–25mm of Hg with maximum changes of about 40-45mm of Hg in few subjects. Hypertensive patients had much greater changes in arterial pressure than normotensives of the same age. Mean increase was 35mm of Hg with excess increase in few patients [14,16].

The duration of laryngoscopy is an important factor affecting the magnitude of pressor response and degree of changes in heart rate. Progressive increase in arterial pressure above awake levels was seen during the first 45 seconds of laryngoscopy. Prolonged laryngoscopy upto 60 seconds produced less than 5mm of Hg additional increase in arterial pressure above the value at 45 seconds as shown by Stoelting [18,19]

The incidence of cardiac arrhythmias ranges from 5 to 90%. Atropine and controlled ventilation decreased the incidence of cardiac arrhythmias. Majority are sinus origin. Other electrocardiographic changes include ventricular premature beats, ST segment depression, increase in PR interval, ventricular tachycardia and ventricular fibrillation.

In patients with raised intracranial pressure, the haemodynamic responses may provoke a further rise in intracranial pressure and the consequences can be in the form of cerebral ischemia, haemorrhage, brain shift and herniation which may be disastrous. It can also cause cerebrovascular accident or a cerebral infarct in patients with cerebrovascular insufficiency. So maintenance of blood pressure and heart rate is of prime importance especially in high risk patients [20].

The increased adrenergic activity and the resultant increase in heart rate and blood pressure were demonstrated by Russel and Prys-Roberts in two separate studies. After intubation, there is a gradual return of blood pressure and heart rate to prelaryngoscopic levels. This may be due to the fatigue of the reflex receptors and subsequent deepening of anesthesia [21,22].

4.1.5 Attenuation of stress Response

Abou *et al* studied the cardiovascular reactions to laryngoscopy and endotracheal intubation following small and large intravenous doses of Lignocaine. The doses were 0.75 mg / kg and 1.5 mg/kg respectively. 1.5mg/kg protected against cardiac arrhythmias of all types, but not the smaller dose. While larger doses provide protection against hypertension and tachycardia, the smaller doses prevented only a rise in systolic blood pressure [23].

During induction of anaesthesia, intravenous Lignocaine reduced autonomic responses to laryngoscopy and intubation as demonstrated in two separate studies by Abou *et al* [2] and Hamill [24].

Asfar *et al* made observations of arterial blood pressure, heart rate and cardiac rhythm during endotracheal intubation and within five minutes thereafter. This was to study the cardiovascular changes following induction and endotracheal intubation and to compare the efficacy of Lignocaine in the dose of 1mg/kg introduced through three different routes, namely laryngotracheal spray, transtracheal injection and intravenous injection. The study showed no significant differences between the groups and the patients who received Lignocaine prior to endotracheal intubation showed minimal cardiovascular changes.[25]

Derbyshire *et al* showed that conventional topical anaesthesia of the mucosa of upper airway is ineffective as a means of ameliorating the pressor and catecholamine responses to routine laryngoscopy and intubation [26].

Stoelting and others found that oropharyngeal topical anaesthesia with viscous Lignocaine 25ml of 2% as a mouth wash or gargle ten minutes prior to laryngoscopy attenuated the pressor response but not tachycardia. This was achieved because viscous Lignocaine superficially anaesthetised those areas in contact with laryngoscope blade, namely epipharynx and laryngopharynx[27]. It was also found that the arterial Lignocaine concentration was less than 0.5 mcg/ml of blood due to minimal absorption and rapid hepatic detoxification. So it was concluded that topical anaesthesia of oropharynx with viscous Lignocaine can be considered to attenuate the pressor response [28].

Sklar *et al* evaluated the effect of Lignocaine inhalation on the circulatory response to direct laryngoscopy and endotracheal intubation. The mean arterial pressure increased by 22.9 mm of Hg in the Lignocaine 40 mg inhalation group, but only an increase of 10.1 mm of Hg was noticed in Lignocaine 120mg inhalation group. Heart rate response to intubation with Lignocaine inhalation was shown to be dose dependant. So inhalation of Lignocaine 120 mg (3ml of 4 %) prior to induction of anaesthesia is effective to attenuate the circulatory responses to laryngoscopy and tracheal intubation [29].

Mostafa *et al* attempted to attenuate the pressor response to laryngoscopy and intubation using direct laryngeal / tracheal Lignocaine spray (Group A) immediately before intubation and by using orolaryngeal Lignocaine spray (Group B) before induction of anaesthesia. An increase in heart rate and diastolic blood pressure was observed in both groups. But systolic blood pressure showed no significant change in Group B. This means topical Lignocaine administration as an oropharyngeal spray before induction is effective in reducing the pressor response to laryngoscopy and intubation [30].

Stoelting in his study noted that blood pressure and heart rate responses to tracheal intubation are minimal when direct laryngoscopy is brief (less than 15 seconds) and when laryngotracheal Lignocaine is injected just before placement of tracheal tube [19].

Scott reported the uses of 10% aerosol spray of Lignocaine to attenuate the pressor response to laryngoscopy and intubation. This is rapidly observed as quickly as if given intravenously. Plasma levels varying 2-5 mcg / ml have observed following the intratracheal administration of 200 mg of Lignocaineas a spray [31]. Youngberg *et al* administered 100 mg Lignocaine (5 ml of 2%) intravenously or 160 mg topically to the larynx to compare the cardiovascular response to intubation between the two techniques. Neither method was completely effective in abolishing hypertension or tachycardia on intubation. More prolonged and more significant increase in pulse rate was observed in the group who received topical Lignocaine. This indicates that intravenous administration of Lignocaine may be superior to the topical administration [32]. Similar findings showing the effectiveness of intravenous Lignocaine was obtained by James *et al* [33].

The optimal time of injection of intravenous Lignocaine prior to tracheal intubation was noted by Tam *et al* [34]. Effects of intravenously administered Lignocaine on cough suppression during tracheal intubation under general anaesthesia were evaluated by Yukioka *et al* [35]. The incidence of coughing reduced significantly when 2 mg/kg of Lignocaine was injected intravenously between one and five minutes before attempting intubation. Cough reflex was suppressed completely by plasma concentration of Lignocaine in excess of 3 mcg/ml. Similar study was undertaken by Poulton [36].

In another study Splinter concluded that both fentanyl 3mcg/kg and Lignocaine 1.5 mg/kg are useful adjuncts during induction with thiopentone to attenuate the haemodynamic responses during intubation [37].

Venus *et al* studied the effects of topical anaesthesia of oropharynx with Lignocaine aerosol (6ml of 4% for five minutes). The pressor response and tachycardia during laryngoscopy and intubation were successfully prevented by Lignocaine aerosol. The incidences of premature ventricular contractions were less when compared to the control group [38].

Steinhaus and others have shown Lignocaine as an effective cough Suppressant [39]. It was shown by Bidawi (1979) that protection from coughing and cardiovascular stimulation with endotracheal extubation is achieved by spraying down the endotracheal tube 60 mg as 4% Lignocaine 3-5 minutes before extubation. Intravenous Lignocaine is a dose dependent central suppressant of cough reflex. The lower cough score was attributed to certain degree of systemic absorption of Lignocaine. Local application of lignocaine results in a slow and rather unpredictable absorption [40].

A study conducted by Baraka showed that administration of 2 mg/kg intravenous Lignocaine effectively prevents laryngospasm during extubation in children undergoing tonsillectomy [41].

The mechanisms by which intravenous Lignocaine prevents bronchoconstriction are

i) Direct inhibition of bronchial smooth muscle
ii) Blocking of the noxious reflex arc.
iii) Stabilization of mast cells and prevention of the release of humoral mediators.

Bidawi and others noticed that intravenous Lignocaine 1mg/kg two minutes prior to extubation prevented the cardiovascular response to extubation[40].

Induction of anaesthesia with propofol 2.5 mg/kg and alfentanil 30 mcg/kg combined with 4 ml of Lignocaine spray 40 mg/ml into the larynx and trachea offered consistent and satisfactory intubation conditions and showed a good protection against cardiovascular effects. Surface analgesia was responsible for this effect [42].

A study by Denlinger *et al* indicated that spraying of the trachea with 4% Lignocaine significantly reduced the pressor response to tracheal intubation [43].

McCoy *et al* in their study compared the McCoy blade to the standard McIntosh blade in regard to changes in Heart rate, Blood Pressure and Plasma catecholamine concentration and found that McCoy blade produced very little changes compared to Macintosh blade [44].

Kaul and Valecha, in their study compared the Pressure response to insertion of LMA to endotracheal intubation and revealed that the tachycardic, hypertensive response as well as the plasma catecholamine concentration were significantly higher in the intubation group than the group with LMA insertion [45].

Takita K *et al* compared the cardiovascular response to endotracheal tube intubation (ETI) with tracheal Lignocaine and placebo and found that tracheal Lignocaine sprayed two minutes before ETI was effective in attenuating the hemodynamic response to ETI than doing intubation without it [46].

De Kock *et al* compared epidural Clonidine to sufentanil in the perioperative period. Patients received epidural Clonidine or sufentanil for 12 hours. Clonidine improved intra operative hemodynamic stability and provided the same amount of postoperative analgesia as did sufentanil. Yet, Clonidine had a longer-lasting residual analgesic effect, thus decreasing postoperative analgesic demands [3].

Costello and Cormack compared Clonidine to temazepam in controlling hemodynamics during pin head-holder application during a craniotomy. Fifty patients took oral Clonidine 3 mcg/kg or oral temazepam 10 to 20 mg given 90 minutes before induction of anesthesia. Clonidine was effective in reducing mean arterial blood pressure increase while pin head-holder application [47].

Laurito *et al* studied the effects of oral Clonidine premedication on sedation and hemodynamic responses during preoperative period, laryngoscopy, and postanesthesia recovery. Patients took Clonidine 100 mcg, Clonidine 200 mcg, triazolam 0.25 mg, or placebo. Oral Clonidine 200 mcg given 90 minutes prior to anesthetic induction effectively sedated and blunted the hemodynamic response, but anxiolytic effects were not seen [48].

Britto *et al* studied clonidine in 20 patients randomized to receive temazepam 10 mg or temazepam 10 mg plus clonidine 3 mcg/kg 45 minutes prior to induction of anesthesia. Clonidine with temazepam 10 mg was superior to temazepam alone in decreasing mean arterial blood pressure, attenuating response to intubation, and providing a better blood-free surgical field [49].

Herman *et al* studied the effect of Clonidine on inhibiting biological effects of catecholamines released during hyperthyroidism. Patients with hyperthyroidism received either nadolol 40 mg twice daily for one week or Clonidine 150 mcg twice daily for one week. Clonidine had similar clinical effects to nadolol[50].

Mikawa Matsuwa *et al* in their study revealed that premediction with oral Clonidine in children attenuated the pressure and tachycardic response to laryngoscopy and tracheal intubation

Mikawa *et al*a conducted a prospective, randomized, double-blind study on 60 children, who were randomized to three groups, (n = 20 for each group) diazepam 0.4 mg per kg (active control), Clonidine 2 micrograms per kg, or Clonidine 4 micrograms per kg per oral. These agents were administered 105 min before induction of anaesthesia and concluded that plasma catecholamine (CA) concentrations increased in response to tracheal intubation in children. Haemodynamic and CA changes were smaller in children receiving Clonidine 4 micrograms per kg ($P < 0.005$) [51].

Zalunardo *et al* did a study on 33 ASA physical status I patients to investigate the effects of intravenous 3 micrograms/kg Clonidine prior to anesthesia induction V/s oral Clonidine 4 micrograms /kg 90 minutes prior to anesthesia induction and concluded that Oral Clonidine at the dose used was less effective in blunting hemodynamic stress response than IV Clonidine[52].

Kulka *et al* in the year 1995 did a randomized double blind study on 48 patients who presented for coronary artery bypass graft (CABG) and compared 0, 2, 4, or 6 micrograms/kg Clonidine as an intravenous (IV) infusion during a 15-min period 30 min prior to induction of anesthesia and concluded that 4 micrograms/kg IV is the appropriate dose to attenuate the stress response to laryngoscopy in CABG patients [53].

Yokota *et al* did the study to compare the effect of oral Clonidine premedication on hemodynamic responses during sedated fiber optic nasal intubation and the study revealed that the oral Clonidine premedication (5 mcg/kg) might contribute to hemodynamic stability during sedated fiber optic nasal intubation[54].

Gupta *et al* studied 60 ASA I/II patients undergoing elective surgery. The patients were divided in to three groups of 20 patients each. Group A received tab Clonidine 0.3 mg 90 min prior to induction along with premedication. Group B received intravenous 1.5 mg/kg Lignocaine 90 seconds prior to induction. Group C received none of these drugs. All patients were induced with ketamine and concluded that oral Clonidine premedication was effective in attenuating the cardiostimulatory response to ketamine while Lignocaine had partial effect [55].

Nishina, Kahoru MD, Mikawa, Katsuya MD, *et al* studied 96 healthy children, 8-13 yr old and concluded oral Clonidine premedication 4 micro gram/kg blunted the increase in heart rate after intravenous atropine in awake children, although Clonidine 2 micro gram/ kg did not. A larger dose of atropine was required to increase the heart rate by 20 beats /min in children receiving the premedicant in the larger dose [56].

Raval *et al* studied 100 ASA Gr I-II patients between 18 and 65 years of age to compare the effectiveness of oral clonidine as a premedicant and attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation with oral diazepam and placebo. They concluded clonidine produced marked sedation and better anxiolysis as compared to placebo, but less sedation and same level of anxiolysis as compared to diazepam. Clonidine provided extra advantage over diazepam and placebo by blunting haemodynamic responses during laryngoscopy and endotracheal intubation and also by its antisialagogue effect [57].

Howie *et al*, studied 54 patients undergoing elective coronary artery bypass graft (CABG) surgery and concluded that Clonidine decreases opioid use and lowers hormonal response while maintaining stable hemodynamics than patients receiving placebo [4].

The baseline pulse rate and blood pressure were identical in both the groups so were the mean blood pressure and the rate pressure product. Pulse rate showed significant reduction in Clonidine group in all the recordings when compared to the Lignocaine group. The systolic blood pressure also showed significant reduction in all the recordings when compared to the Lignocaine group. The combined effect of reduced pulse rate and systolic blood pressure resulted in greater reduction in rate pressure product in the Clonidine group. Maximum reduction was noted after induction in Clonidine group. It was able to keep the rate pressure product below the preinduction value where as it was not like so with Lignocaine.

The analgesic properties of Clonidine are due to its action on the central alpha-2 adrenergic receptors while its effects on cardiovascular system are due to combined action on central alpha-2, peripheral alpha-1 and alpha-2 receptors. The fall in blood pressure is due to its effect of reduced sympathetic activity as reflected by reduced plasma concentrations of noradrenaline. The slowing of heart rate, increased vagal tone and sedation caused by Clonidine premedication are due to its effects on the preganglionic sympathetic fibres where it reduces the discharge and stimulation of parasympathetic outflow. The net effect is to produce a decrease in heart rate, cardiac output and systemic vascular resistance leading to reduction in blood pressure. In this present study also Clonidine reduced the baseline pulse and systolic blood pressure [7, 9].

Though Lignocaine reduces cardio vascular responses to laryngoscopy and intubation, present study shows that Clonidine is superior to Lignocaine in attenuating the pressor response.

The cardiovascular effects of Clonidine are dose dependent. In the previous studies Clonidine showed significant reduction in heart rate and blood pressure when it was given in the dose of 5mcg per kg whereas it didn't show much reduction when given in 3 mcg per kg dose [8]. In the present study Clonidine was given in the doses of 4-5 mcg per kg which showed significant reduction in both heart rate and blood pressure consistent with previous studies which compared the dose related effects of Clonidine.

One of the concerns in Clonidine administration is the risk of Clonidine withdrawal and associated hyper dynamic cardiovascular states. Several reports had shown that short term administration of Clonidine does not induce withdrawal syndrome. Rebound phenomenon or untoward haemodynamic events after the sudden withdrawal of Clonidine therapy can occur only after 6-30 days of Clonidine administration [58].

This study showed significant difference in attenuating the haemodynamic response for laryngoscopy and intubation between Lignocaine and Clonidine with Clonidine reducing the rate pressure product more than the Lignocaine throughout the study period. The reduced heart rate and rate pressure product with Clonidine premedication there by optimize the myocardial oxygen supply-demand relationship.

5.Conclusion

Oral Clonidine has better control over haemodynamic response to laryngoscopy and intubation when compared to Lignocaine given in dose of 4-5 mcg per kg.

The reduction in heart rate and blood pressure by Clonidine premedication was stable during the initial seven minutes after intubation (study period).

References

[1] King BD, Harris LC,Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during anaesthesia. *Anaesthesiology* 1951; 12:556-566.

[2] Abou Madi MN, Keszler H, Yacoub JM. A method of prevention of cardiovascular reaction to larygoscopy and intubation. *Can Anaesth Soc J*. 1975; 22:316.

[3] De Kock M, Famenne F, Deckers G *et al*, Epidural clonidine or sufentanil for intraoperative and postoperative analgesia. *Anesth Analg*. 1995; 81:1154-1162.

[4] Howie MB, Hiestand DC, Jopling MW, Effects of oral clonidine, premedication on anesthetic requirement, hormonal response, hemodynamics and recovery in coronary artery bypass graft surgery patients. *J Clin Anesth* 1996 Jun; 8(4):263-72.

[5] Engelman E, Lipszyc M, Gilbart E, *et al*. Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; 71: 178-187.

[6] Flacke JW, Bloor BC, Flacke WE, *et al*. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; 67: 11- 19.

[7] Stoelting Robert K. Pharmacology and physiology in anesthetic practice.3rd ed. Philadelphia, New York. Lippincott-Raven.1999.p158-178,304-307.

[8] Carabine U.A., Wright P.M.C and Moore J. Preanaesthetic medication with clonidine: A dose response study. *Br J Anesth* 1991; 67:79-83.

[9] Lowenthal, D.T., Matzek, K.M., and Mac Gregor, T.R, Clinical pharmacokinetics of clonidine. *Clin pharmacokinet*, 1988; 14: 287- 310.

[10] Miller Ronald D, Miller's Anesthesia, 6th ed, Philedelphia, Churchill livingstone, 2005: 2730-31.

[11] Tomori Z, Widdicombe JG. Muscular bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of respiratory tract. *JI Physiology*; 1969:200:25.
[12] Shribman AJ, Smith G. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. *Br J Anaesth.*1987; Mar 59(3):295-299.
[13] Wycoff CC. Endotracheal intubation: Effect of blood pressure and pulse rate. *Anaesthesiology*.1960; 21:153.
[14] Takeshema, Node K. Cardiovascular response to rapd anaesthsia induction and endotracheal intubation. *Anaesth Analg Current Research* 1964; 43:201.
[15] Dingle HR. Antihypertensive drugs. *Anaesthsia* 1966; 21:151.
[16] Forbes AM,Dally FG. Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. *Br J Anaesth.* 1970; 42:618.
[17] Fox EJ, Sklar GS. Complication related to pressor response to endotracheal intubation. *Anaesthesiology*.1977; 44:524-526.
[18] Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. *Anaesthesiology*. 1977; Oct 47 (4):381-384.
[19] Stoelting RK. Blood pressure and heart rate changes during short term laryngoscopy for tracheal intubation: Influence of viscous or intravenous lidocaine. *Anaesth Analg* 1978; mar57 (2):197-199.
[20] Robert G. Burney, Richard Winn. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia. *Anesth Analg* 1975; 54:687-690.
[21] Russel WJ, Morris RG. Changes in plasma catecholamine concentrations during endotracheal intubation. *Br J Anaesth.*1981; 53:837-839.
[22] Prys-Roberts C, Greene LT, Foex P. Studies of anaesthesia in relation to hypertension II: Haemodynamic consequences of induction and endotracheal intubation. *Br J Anaesth* 1971; 43:531.
[23] Abou Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous dose of lidocaine. *Can Anaesth Soc J*. 1977; Jan 24 (1):12-19.
[24] Hamill JF,Bedforde RF,Weaver DC. Lidocaine before endotracheal intubation intravenously or laryngotracheal. *Anaesthesiology* 1981; 55:578-579.
[25] Asfar SN, Abdulla WY. The effect of various administration routes of lidocaine on haemodynamics and ECG rhythm during endotracheal intubation. *Acta Anaesth Belg*. 1990; 41(1):17-24.
[26] Derbyshire DR, Smith G. Effect of topical lignocaine on sympathoadrenal responses to tracheal intubation. *Br J Anaesth.* 1987; Mar 59 (3):300-304.
[27] Kautto UM, Heinonen J. Attenuation of circulatory responses to laryngoscopy and tracheal intubation. A comparison of two methods of topical anaesthesia. *Acta Anaesthesiol Scand.*1982; Dec 26 (6):599-602.
[28] Stoelting RK. Circulatory response to laryngoscopy and tracheal intubation with or without prior oropharyngeal viscus lidocaine. *Anaesth Analg* 1977 Sep; 56(5):618-621.
[29] Sklar BZ, Lurie S.Lidocaine inhalation attenuates the circulatory response to laryngoscopy and endotracheal intubation. *J Clin Anaesthesia*.1989; July36 (4):370-376.
[30] Mostafa SM, Barrett PJ, Mcttugh P. Comparison of the effects of topical lignocaine spray applied before or after induction of anaesthesia in the pressor responses to direct laryngoscopy and intubation. *Eur J Anaesthesiology*.1999 Jan; 16(1):7-10.
[31] Scott DB, Littlewood DG. Plasma lignocaine concentration following endotracheal spraying with an aerosol. *Br J Anaesth.* 1976; 48:899.
[32] Youngberg JA, Graybar G, Hutchings D. Comparision of intravenous and topical lignocaine in attenuating cardiovascular responses to endotracheal intubation. *South Med J*. 1983; Sep76 (9):1122-1124.
[33] James F, Hamlil MD,Robert F. Lignocaine before endotracheal intubation: intravenous or laryngotracheal spray. *Anaesthesiology* 1981; 55:578.
[34] Tam S, Campbell M. Attenuation of circulatory responses to endotracheal intubation using intravenous lidocaine: A determination of optimal time of injection. *Anaesth Analg* 1987; 66:1036-38.
[35] Yukoika H, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anaesth Analg.* 1985; Dec 64(12):1189-1192.
[36] Poulton TJ, James FM. Cough suppression by lignocaine. *Anaesthesia* 1979; 50:470-472.
[37] Splinter FM, Crevenkof. Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: Effects of fentanyl, lidocaine and thiopentone. *Can J Anaesth* 1989 July; 36(4):370-376.
[38] Vnus B, Polassani V, Pharm G. Effects of aerosolized lidocaine on circulatory responses to laryngoscopy and tracheal intubation. Crit Care Med.1984; Apr 12(4):391-394.
[39] Steinhause JE, Gaskin L. A study of lidocaine as suppressant of cough reflex. *Anaesthsiology*.1963; 24:285-290.
[40] Bidawi AVC, Bidwani VA. Blood pressure and pulse rate response to extubation with or without prior topical tracheal anaesthesia.1979; 25:416.
[41] Baraka A. Intravenous lignocaine controls extubation laryngospasm in children. *Anaesth Analg* 1978; 57:506.
[42] Bulowk, Lund J. the effect of topical on intubating conditions after propofol -alfentanil induction. *Acta Anaesthesiol Scand*. 1996; 40:752-756.

[43] Denlinger JK, Ellison N. Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. *Anaesthesiology*. 1974 Oct; 41:409-412.

[44] McCoy E.P EP, Mirakhur RK, Mccloskey. A comparison of stress response to laryngoscopy, The Macintosh Vs The Mc Coy Blade *Br J Anaesth* 1995; 50: 943-946.

[45] Kaul Tej, Veena Valecha *et al*. Catecholamine responses to Endotracheal intubation and Laryngeal Mask Airway Insertion. *Indian J Anaesth*; 1999: (43):30.

[46] Takita K, Morimoto Y, Kemmotsu O. Tracheal lidocaine attenuates the cardiovascular response to endotracheal intubation. *Can J Anaesth* 2001 Sep; 48(8):7326.

[47] Costello TG, Cormack JR. Clonidine premedication decreases hemodynamic responses to pin head-holder application during craniotomy. *Anesth Analg*. 1998; 86:1001-1004.

[48] Laurito C.E., Baughman V.L. Becker G.L *et al*. Oral clonidine blunts the haemodynamic responses to brief but not prolonged laryngoscopy. *J Clin Anaesth*. 1993; Jan–Feb 5(1):54-7.

[49] Britto JA, McCoy D, Fourie LR. Clonidine as premedication for rhinoplasty. *Plast Reconstr Surg*. 1997; 100:548-549.

[50] Herman VS, Joffe BI, Kalk WJ, *et al*. Clinical and biochemical responses to nadolol and clonidine in hyperthyroidism. *J Clin Pharmacol* 1989; 29:1117-1120.

[51] Mikawa K, Nishina K, Maekawa N *et al*. Attention of the catecholamine response to tracheal intubation with oral clonidine in children. *Can J Anesth*, 1995; 42: 869-874.

[52] Zalunardo MP, Zollinger A, Spahn DR *et al*. Effects of intravenous and oral clonidine on hemodynamic and plasma-catecholamine response due to endotracheal intubation. *PMID*: 9075040.

[53] Kulka PJ, Tryba M, Zenz M. Dose response effects of intravenous clonidine on stress response during introduction of anesthesia in coronary artery bypass graft patients. *Anest. Analg* 1995; 80: 263-268.

[54] Yokota S, Komatsu T, Yano K *et al*: Effect of oral clonidine premedication on hemodynamic responses during sedated nasal fibreoptic intubation. *Nagoya J. Med Sci;* May 1998:61:47-52.

[55] Gupta P. K., Sehgal R., Gupta M *et al*. Attenuation of cardiovascular responses to ketamine: comparative evaluation of clonidine. *Indian J Anaesth. 2002*; 46 (6) : 457-459.

[56] Nishina, Kahoru MD, Mikawa *et al*. Oral Clonidine Premedication Blunts the Heart Rate Response to Intravenous Atropine in awake Children. *Anesthesiology*.1995; 82(5):1126-1130.

[57] Raval Dipak L., Mehta Malini K. Oral clonidine premedication for attenuation of haemodynamic response to laryngoscopy and intubation. *Indian J Anaesth.* 2002; 46 (2): 124-129.

[58] Das AK, Rudra R. Clinical efficacy of oral clonidine as a preanaesthetic medicant. *Indian J Anaesth.*1995; 43:133-139.