A COMPARATIVE STUDY ON THREE DOSES OF ESMOLOL TO ATTENUATE THE HEMO DYNAMIC STRESS RESPONSE DURING LARYNGOSCOPY AND ENDO TRACHEAL INTUBATION

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CHENNAI, TAMILNADU

MARCH 2O1O

CERTIFICATE

This is to certify that this dissertation titled **"A COMPARATIVE STUDY ON THREE DOSES OF ESMOLOL TO ATTENUATE THE HEMO DYNAMIC STRESS RESPONSE DURING LARYNGOSCOPY AND ENDO TRACHEAL INTUBATION"** has been prepared by Dr.M.Mahendran under my supervision in the Department of Anaesthesiology, Chengalpattu Medical College and Hospital, Chengalpattu during the academic period 2007-2010 and is being submitted to the Tamil Nadu DR.M.G.R. Medical University, Chennai in partial fulfillment of the University regulation for the award of the Degree of Doctor of Medicine (Branch-X MD Anaesthesiology) and his dissertation is a bonafide work.

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DECLARATION

I, Dr. M.Mahendran, solemnly declare that the dissertation "**A COMPARATIVE STUDY ON THREE DOSES OF ESMOLOL TO ATTENUATE THE HEMO DYNAMIC STRESS RESPONSE DURING LARYNGOSCOPY AND ENDO TRACHEAL INTUBATION**" is a bonafide work done by me in the Department of Anaesthesiology, Chengalpattu Medical College and Hospital, Chengalpattu, after getting approval from the Ethical Committee, under the able guidance of **Prof.Dr.R.S.VIJAYALAKSHMI,** MD., DA., Professor and HOD, Department of Anaesthesiology, Chengalpattu Medical College, Chengalpattu.

Place: Chengalpattu.

Date:

(Dr .M.Mahendran)

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CONTENTS

INTRODUCTION

In 1940, Reid and Brace first described hemodynamic response to laryngoscopy and intubation.

Laryngoscopy and endotracheal intubation are mandatory for most patients undergoing general anaesthesia, which is invariably associated with certain cardiovascular changes such as tachycardia or bradycardia, rise in blood pressure and a wide variety of cardiac arrhythmias. These effects are deleterious in susceptible individuals culminating in perioperative myocardial ischemia, acute heart failure and cerebrovascular accidents. The hemodynamic response to laryngoscopy and endo tracheal intubation has been recognized since 1951. The induction of anaesthesia, laryngoscopy and intubation and surgical stimulation often evoke cardiovascular response characterized by alterations in systemic arterial pressure, pulse rate and cardiac rhythm. The response following laryngoscopy and intubation peaks at 1.2 minute and returns to normal within 5 – 10 minutes.

Though these sympathoadrenal response are probably of little consequence in healthy individuals, it is hazardous to those patients with hypertension, coronary heart disease, intra cranial pathology and hyper

reactive airways. In such cases, reflex circulatory response such as increase in heart rate, systemic arterial blood pressure and disturbances in cardiac rhythm needs to be suppressed. Prof. King et al (1951) documented myocardial ischemic changes due to reflex sympthoadrenal response immediately following laryngoscopy and intubation with a mean rise in systemic pressure of 40 mm Hg even in normotensive individuals.

Various systemic as well as topical agents were used to reduce these untoward hemodynamic responses due to laryngoscopy and intubation. Those technique which require prior laryngoscopy to the local anaesthetic solution are likely to be of limited value. The common strategies adopted are narcotics, vasodilators, beta blockers, calcium channel blockers, lidocaine other sympatholytics.

IV Esmolol due to its ultra short action seem to be ideal to control intense but brief sympathetic stimulation following endotracheal intubation.

Hence, the above study was done in the Department of Anaesthesiology, Chengalpattu Medical College, Chengalpattu.

AIM

The hemodynamic response during laryngoscopy and intubation should be abolished to balance the myocardial oxygen supply and demand for the safe conduct of anaesthesia. This study was done to compare the varying doses of IV Esmolol in attenuating the hemodynamic stress response to laryngoscopy and endo tracheal intubation.

PATHOPHYSIOLOGY OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

Intubation of trachea alters the respiratory and cardiovascular physiology by both reflex response and by physical presence of endo tracheal tube. Although reflex responses are generally of short duration and of little consequence in majority of patients, they may produce profound disturbance in patients with underlying abnormalities such as hypertension, coronary heart disease, reactive airways, intra cranial pathology.

CARDIOVASCULAR RESPONSES:

The cardiovascular responses to laryngoscopy and intubation are bradycardia, tachycardia, hypertension, and they are mediated by both the sympathetic and parasympathetic nervous system. Bradycardia is often seen in infants and small children during laryngoscopy and intubation. Although only rarely seen in adults this reflex is mediated by increase in vagal tone at sinoatrial node and is virtually a monosynaptic response to a noxious stimuli in airway.

The more common response to endotracheal intubation is hypertension and tachycardia mediated by sympathetic efferent via the cardioaccelerator nerves and sympathetic chain ganglia. The polysynaptic nature of pathways from IX and X nerve afferents to sympathetic nervous

system.via the brain stem and spinal cord in a diffuse autonomic response which includes widespread release of norepinephrine from adrenal nerve terminals and adrenal medulla.

Some of the hypertensive response to endotracheal intubation also results from activation of renin angiotensin system, with release of renin from the renal juxta glomerular apparatus and end organ innervated by beta adrenergic nerve terminals.

The effects of endotracheal intubation on the pulmonary vasculature are less well understood then the responses elicited in the systemic circulation. They are often coupled with the changes in airway reactivity associated with intubation. They are i) glottis closure reflex (laryngospasm due to brisk motor response), ii) decrease in dead space, iii) increase in airway resistance, iv) bronchospasm (a reflex response to iintubation), v) removal of glottic barrier and may reduce lung volume, vi) cough efficiency is reduced.

METHODS TO ATTENUATE CIRCULATORY RESPONSE DURING LARYNGOSCOPY AND INTUBATION

The balance between myocardial oxygen supply and demand must be preserved to minimize the risk of peri operative ischemia and infarction.

Factors affecting myocardial oxygen demand and supply.

Demand

Basal requirement

Heart rate

Wall tension – preload, afterload

Contractility

Supply

Heart rate – depends on diastolic time, hence decreases in heart rate, more diastolic time, more the oxygen supply to myocardium.

Coronary Perfusion Pressure – depends on Aortic diastolic pressure and ventricular end diastolic pressure and increase with high aortic diastolic pressure and low ventricular end diastolic pressure.

Arterial oxygen content – depends on arterial oxygen partial pressure and haemoglobin concentration.

Coronary vessel diameter.

Numbers of methods were used to attenuate cardiovascular response due to laryngoscopy and intubation.

1. Deepening of General Anaesthesia :

Inhalational agents 'MAC' (i.e.) the dose of volatile agent required to blunt the cardiovascular responses to laryngoscopy and intubation. This deep level is achieved by inhalational agents result in profound cardiovascular depression prior to laryngoscopy and intubation. Various agents used are Halothane, Isoflurane, Sevoflurane.

2. Lidocaine :

- Lidocaine gargle for oropharyngeal anaesthesia.
- Aerosol for intra tracheal anaesthesia
- Topical spray for vocal cords
- Regional nerve blocks – Superior Laryngeal nerve, Glossopharyngeal nerve
- Intra venous bolus of systemic anaesthesia
- Topical anaesthesia of upper airway has proven to be less effective than systemic administration of lidocaine.

Mechanism of action

By increasing the depth of General Anaesthesia

Potentiation of effects of Nitrous Oxide and reduction of MAC of Halothane by 10 – 28 %

Direct cardiac depressant

Peripheral vasodilation

Antiarrhythmic properties

Suppression of cough reflex

3. Vasodilators

Hydralazine, Sodium nitro prusside, Nitroglycerine

4. Narcotics

Fentanyl, Alfentanil, Sufentanil, Pethidine, Morphine.

Fentanyl is most common used narcotic agent. It is a potent analgesic, has short duration of action does not increase intra cranial tension, and has minimal circulatory changes.

Mechanism of action

Suppression of Nociceptive stimulation caused by Intubation

Centrally mediated decrease in sympathetic tone

Activation of vagal tone.

5. Adrenergic blockers

Long acting – Metoprolol, Phentolamine, Proponalol, Labetalol

Short acting – Esmolol.

Most commonly used agent because of its ultrashort action. It decreases heart rate, ejection fraction, and cardiac index but maintains coronary perfusion pressure.

6. **Calcium Channel Blockers**

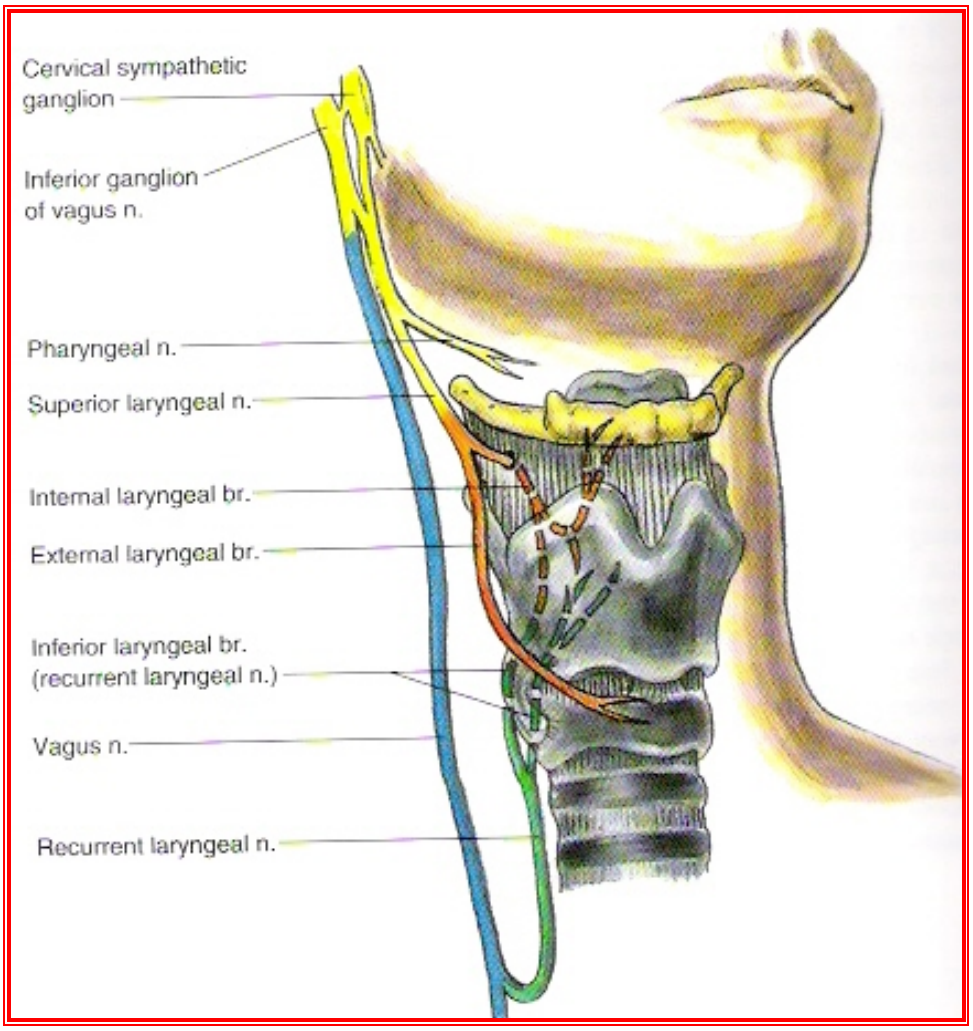
   Nifedipine, Nicardipine,- has got superior action

   Verapamil, Diltiazem

7. **Alpha 2 agonist-Clonidine**

8. **Midazolam – Sedative & Anxiolytic**

9. **Magesium Sulphate - Sedative & Anxiolytic**


Cervical sympathetic ganglion
Inferior ganglion of vagus n.
Pharyngeal n.
Superior laryngeal n.
Internal laryngeal br.
External laryngeal br.
Inferior laryngeal br. (recurrent laryngeal n.)
Vagus n.
Recurrent laryngeal n.

NERVE SUPPLY OF LARYNX

Nerve supply of the larynx is from the Vagus nerve by way of its superior laryngeal nerve and recurrent laryngeal branches. The Superior Laryngeal nerve arises from the inferior ganglion of Vagus and receives branch from the Superior cervical sympathetic ganglion. The external branch provides motor supply to the cricothyroid muscle while the internal branch pierces the thyrohyoid membrane and divides into two main sensory and secretomotor branches. The upper branch supplies the mucous membrane of lower part of pharynx, epiglottis, vallecula and vestibule of larynx. The lower branch supplies the aryepiglottic fold and mucous membrane down to the level of vocal folds.

The internal branch of superior laryngeal nerve supplies the supraglottic area.

The Recurrent laryngeal nerve ascends to the larynx in the groove between the oesophagus and trachea and divides into motor and sensory branches.

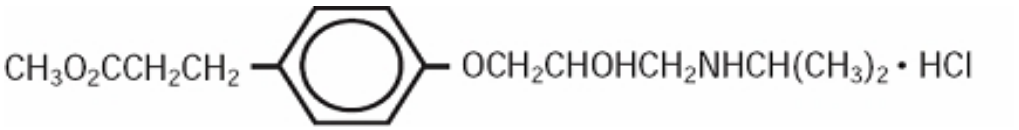
The motor branch has fibres derived from the cranial root of the accessory nerve which supplies all the intrinsic muscles of larynx except the cricothyroid.

The sensory branch supplies the laryngeal mucous membrane below the level of vocal folds.

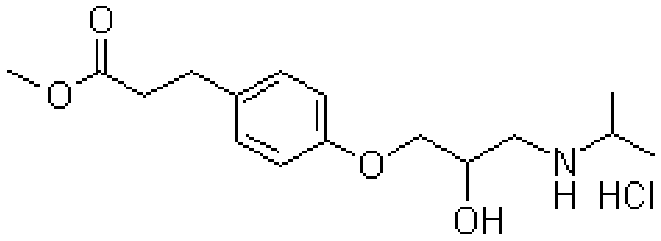

NDC 63323-652-10
605210
ESMOLOL HYDROCHLORIDE
INJECTION
100 mg/10 mL
(10 mg/mL)
For Intravenous Use
Rx only
10 mL
Single Dose Vial
Preservative Free

PHARMACOLOGY OF ESMOLOL

Esmolol hydrochloride is a beta1-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes). The chemical name for Esmolol hydrochloride is (±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride and it has the following structure:



Esmolol hydrochloride has the molecular formula C16H26NO4CI and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair.



Esmolol HCl Injection is a clear, colourless to light yellow, sterile, nonpyrogenic solution. 100 mg, 10 mL Single Dose Vial - Each mL contains 10 mg Esmolol Hydrochloride and Water for Injection.

Esmolol - Clinical Pharmacology [1,2]

Esmolol hydrochloride is a beta1-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol inhibits the beta1 receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta2 receptors located chiefly in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism

Esmolol hydrochloride is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylchoIinesterase. Total body clearance in man was found to be about 20 L/kg/hr, which is greater than cardiac output; thus the metabolism of Esmolol is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmolol has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.

Because of its short half-life, blood levels of Esmolol can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.

Consistent with the high rate of blood-based metabolism of Esmolol, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, approximately 73% to 88% of the dosage has been accounted for in the urine as the acid metabolite of Esmolol.

Metabolism of Esmolol results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of Esmolol and in normal volunteers its blood levels do not correspond to the level of beta blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about ten-fold that of normals, and plasma levels considerably elevated.

Esmolol has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

PHARMACODYNAMICS

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of Esmolol hydrochloride, showing reduction in heart rate at rest and during exercise, and attenuation of Isoproterenol-induced increases in heart rate. Blood levels of Esmolol

have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10 to 20 minutes.

In human electrophysiology studies, Esmolol produced effects typical of a beta blocker; a decrease in the heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing, and an increase in antegrade Wenckebach cycle length.

During exercise, Esmolol produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by Propranolol, but produced a significantly larger fall in systolic blood pressure.

At thirty minutes after the discontinuation of Esmolol infusion, all of the hemodynamic parameters had returned to pre-treatment levels.

Esmolol produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and Esmolol was well tolerated by asthmatic patients.

No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of Esmolol.

Compatibility with Commonly Used Intravenous Fluids

Esmolol was tested for compatibility with ten commonly used intravenous fluids at a final concentration of 10 mg Esmolol Hydrochloride per ml. Esmolol was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

1. Dextrose (5%) Injection,
2. Dextrose (5%) in Lactated Ringer's Injection
3. Dextrose (5%) in Ringer's Injection
4. Dextrose (5%) and Sodium Chloride (0.45%) Injection,
5. Dextrose (5%) and Sodium Chloride (0.9%) Injection,
6. Lactated Ringer's Injection,
7. Potassium Chloride (40 mEq/liter) in Dextrose (5%) Injection,
8. Sodium Chloride (0.45%) Injection,
9. Sodium Chloride (0.9%) Injection,
10. Esmolol is NOT compatible with Sodium Bicarbonate(5%) Injection.

SIDE EFFECTS

Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension.

Cardiovascular

Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during Esmolol infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

Central Nervous System

Dizziness has occurred in 3% of patients; somnolence in 3%; confusion, headache, and agitation in about 2%; and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients, with one death.

Respiratory

Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

Gastrointestinal

Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

Skin (Infusion Site)

Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

Miscellaneous

Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

DRUG INTERACTIONS

1. Catecholamine-depleting drugs, e.g., Reserpine, may have an additive effect when given with beta blocking agents. Patients treated concurrently with Esmolol and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

2. A study of interaction between Esmolol and Warfarin showed that concomitant administration of Esmolol and Warfarin does not alter warfarin plasma levels. Esmolol concentrations were equivocally higher when given with Warfarin, but this is not likely to be clinically important.

3. When Digoxin and Esmolol were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect Esmolol pharmacokinetics.

4. When intravenous Morphine and Esmolol were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but Esmolol steady-state blood levels were increased by

46% in the presence of morphine. No other pharmacokinetic parameters were changed.

5. The effect of Esmolol on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by Esmolol, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.

6. Although the interactions observed in these studies do not appear to be of major clinical importance, Esmolol should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

7. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

8. Caution should be exercised when considering the use of Esmolol and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, Esmolol should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because

of the danger of blocking cardiac contractility when systemic vascular resistance is high.

WARNINGS

Hypotension

In clinical trials 20-50% of patients treated with Esmolol have experienced hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Esmolol should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

Cardiac Failure

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, Esmolol should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Esmolol, specific treatment may also be considered. The use of Esmolol for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of the effects of Esmolol, several cases of death have been reported in complex clinical states where Esmolol was presumably being used to control ventricular rate.

Bronchospastic Diseases

Patients with Bronchospastic diseases should, in general, not receive beta blockers. Because of its relative $beta_1$ selectivity and titratability, Esmolol may be used with caution in patients with bronchospastic diseases. However, since beta1 selectivity is not absolute,

Esmolol should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a $beta_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

Diabetes Mellitus and Hypoglycemia

Esmolol should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

PRECAUTIONS

1. General:

Because the acid metabolite of Esmolol is primarily excreted unchanged by the kidney, Esmolol should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

2. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with Esmolol.

3. Pregnancy:

Teratogenicity studies in rats at intravenous dosages of Esmolol up to 3000 mcg/kg/min (3 mg/kg/min) (ten times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women, use of Esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. Esmolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4. Nursing Mothers

It is not known whether Esmolol is excreted in human milk; however, caution should be exercised when Esmolol is administered to a nursing woman.

5. Pediatric Use

The safety and effectiveness of Esmolol in pediatric patients have not been established.

OVERDOSE

Acute Toxicity

Overdoses of Esmolol can cause cardiac arrest. In addition, overdoses can produce bradycardia, hypotension, electromechanical dissociation. Cases of massive accidental overdoses of Esmolol have occurred due to dilution errors. Use of Esmolol Premixed Injection and Esmolol Double Strength Premixed Injection may reduce the potential for dilution errors. Some of these overdoses have been fatal while others resulted in permanent disability. Bolus doses in the range of 625 mg to 2.5 g (12.5-50 mg/kg) have been fatal. Patients have recovered completely from overdoses as high as 1.75 g given over one minute or doses of 7.5 g given over one hour for cardiovascular surgery. The patients who survived appear to be those whose circulation could be supported until the effects of Esmolol resolved.

Because of its approximately 9-minute elimination half-life, the first step in the management of toxicity should be to discontinue the Esmolol infusion. Then, based on the observed clinical effects, the following general measures should also be considered.

Bradycardia: Intravenous administration of atropine.

Bronchospasm: Intravenous administration of a $beta_2$ stimulating agent and/or a theophylline derivative.

Cardiac Failure: Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine, isoproterenol, or amrinone may be considered.

Symptomatic Hypotension: Intravenous administration of fluids and/or pressor agents.

CONTRAINDICATIONS

Esmolol is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure

REVIEW OF LITERATURE

Though laryngoscopy and intubation were done with ease in yester years, the anaesthesiologist had to struggle to combat or subdue the circulatory or cardiovascular effects of the said procedure in patients with compromised circulatory system. Endotracheal intubation cause a reflex mediated increase in sympathetic activity in anesthetized patients. Enhanced sympathetic activity causes an increase in plasma catecholamine concentrations, blood pressure, heart rate, and myocardial oxygen demand.

King et al (1957)[4] used deep Ether anaesthetic to abolish the reflex circulatory response to tracheal intubation.

Ebert TJ et al[5] (1989) studied that circulatory response to laryngoscopy comparing the effects of Esmolol and Fentanyl and they concluded that heart rate response to laryngoscopy was more effectively blocked by Fentanyl while Esmolol better retained coronary perfusion pressure. There were no complications or ischemic ECG changes in any patient.

Ebert TJ and Bernstein JS (1990)[6] studied that hemodynamic response to Rapid sequence induction and intubation in healthy patients with a single bolus dose of Esmolol. They concluded that Esmolol 2 mg/kg bolus effectively attenuated heart rate, systolic blood pressure, diastolic blood pressure, rate pressure product increases produced by laryngoscopy and intubation.

Sheppard et al[7] (1990) compared different bolus dose of Esmolol and concluded that attenuation of intubation response is adequate following 100 mg of Esmolol.

Helfman SM et al[9] (1991) compared the efficacy of Lidocaine , Fentanyl, Esmolol to obtund the intubation responses and concluded that only Esmolol provided constant and reliable part against increase in heart rate and systolic blood pressure accompanying laryngoscopy and intubation.

Miller D.R et al (1991)[10] in their Canadian multicentre trial involving 548 patients concluded that 100 mg bolus Esmolol is safe and effective agent. This dose of Esmolol combined with low dose of Fentanyl (2-3mcg/kg) results in effective control of both heart rate and blood pressure while avoiding important side effect.

Vucovic M et al (1992)[11] concluded randomized control trial with 500 mcg/kg/min for 2 minutes and maintenance 100 mcg/kg/min till

intubation and showed that heart rate , systolic blood pressure were significantly decreased in Esmolol group.

Ganbatz C.L et al [11] (1991) also had similar results of Miller D.R et al., Parnan S.M et al (1990) also concluded that single bolus dose of Esmolol is effective in obtunding intubation response.

Vucovic M et al[12] (1992) studied about the use of Esmolol for management of cardiovascular responses to laryngoscopy and tracheal intubation and found that pressor response to laryngoscopy was significantly less marked in patients given Esmolol 2 minutes before intubation.

Chung KS et al[13] (1992) studied or comparison of Fentanyl, Esmolol and their combination for blunting the hyper dynamic responses during Rapid sequence intubation and concluded that a combination of low dose Fentanyl and Esmolol provides on attenuation to a higher dose of Fentanyl for blunting the hyper dynamic response to laryngoscopy and intubation.

Kovac et al (1992)[14] concluded that in an eye patient with coronary artery disease, or in any patient whom increase in heart rate may be detrimental, Esmolol may be a useful adjunct in combination with low dose alfentanil to attenuate the increase in heart rate due to laryngoscopy and intubation.

Yuan L,Chia YY (1994)[15] studied the efficiency of bolus dose Esmolol in blunting the stress response comparing 100 mg Esmolol versus 200 mg Esmolol. They concluded that both bolus dose of Esmolol could effectively attenuate the increase the heart rate, hypertension produced by laryngoscopy and intubation, furthermore, Esmolol 200 mg presented a better hemodynamic stability than100 mg Esmolol.

Sharma S, Ghania A (1995)[16] also concluded adequate hemodynamic control was obtained with the administration of Esmolol bolus 2mg/kg.

Weist. D et al (1995)[17] made a review of therapeutic efficacy and pharmacokinetic characteristics of Esmolol.

Singh H et al (1995)[18] in their study concluded that Lidocaine 1.5 mg/kg IV and Nitroglycerine 2 mcg/kg IV were effective in controlling the acute hemodynamic response following laryngoscopy and intubation. Esmolol 1.4 mg/kg was significantly more effect than either Lidocaine or Nitroglycerine in controlling heart rate or mean arterial pressure increase during intubation.

Sharma et al[19] (1996) compared the ability of different bolus doses of Esmolol to blunt the hemodynamic response to laryngoscopy and intubation in treated hypertensive patients. Concluded that Esmolol 100mg given as bolus is effective as well as safe in blunting the response.

Feng C.K et al [20](1996) concluded that Esmolol only could reliably offer protection against increase in both heart rate and systolic blood pressure. Low dose Fentanyl (2 mcg/kg) prevented heart rate but not increase in heart rate and 2 mg/kg lidocaine had no effect.

Kindler, CH, Schumacher PG[21] (1996) studied the hemodynamic response to intubation with Lidocaine 1.5 mg/kg, Esmolol 1 mg/kg, Esmolol 2 mg/kg ,combination of Lidocaine 1.5 mg/kg and Esmolol 1 mg/kg and concluded that Esmolol 1-2 mg/kg is reliably effective in attenuating the heart rate response to tracheal intubation. Neither of the two doses of Esmolol tested nor that of Lidocaine attenuated the blood pressure response. Only the combination of Lidocaine and Esmolol attenuated the heart rate and blood pressure response to tracheal intubation.

Wang L et al[22] (1999) concluded that 1.2 mg/kg bolus of Esmolol is effective and safe.

Atlee JL et al[23] (2000) compared the efficacy of Esmolol, Nicardipine, or their combination to blunt the hemodynamic response after intubation and found that the peak increase in blood pressure is blunted by a combination of Esmolol and Nicardipine. No single drug or combination opposed increase in heart rate.

Bensky et al (2000)[24] in their study concluded that small dose of Esmolol may block the increase in heart rate and blood pressure resulting from laryngoscopy and intubation.

Figueredo, E.Garcia- Fuentes EM (2001)[25] compared the results of 38 randomized control trial involving different regimen and doses of Esmolol and found that the most effective regimen was a loading dose of 500 mcg/kg/min over 4 minute, followed by continuous infusion dose of 200-300 mcg/kg/min.

Levitt M.A., Dresden GM (2001)[26] studied the efficacy of Esmolol versus Lidocaine to attenuate the hemodynamic response to intubation in isolated head trauma patients and concluded that both have similar effects.

S. Bansal et al (2002)[27] studied the effect of IV Esmolol with or without Lidocaine in attenuating hemodynamic response in patients with PIH and concluded that Esmolol 1 mg/kg with Lidocaine 1.5 mg/kg is effective in attenuating adrenergic response to laryngoscopy and intubation.

Tan PH et al (2002) [28] made a study on combined use of Esmolol and Nicardipine to blunt the hemodynamic response and found that patients receiving Esmolol 1mg/kg and Nicardipine 30 mcg/kg showed no significant change is systolic blood pressure after tracheal intubation compared with baseline.

Fernandez – Gatinski S et al[29] (2004) compared the effects of Clonidine, Esmolol, Alfentanil on the level of hypnosis and hemodynamic response to laryngoscopy and intubation and concluded that none of the study drugs blocked the increase in MAP induced by endotracheal intubation but Esmolol provided better overall hemodynamic stability. All groups had an adequate level of hypnosis.

MATERIALS AND METHODS

Sixty ASA I & II patients undergoing elective surgical procedure under general anaesthesia with endotracheal intubation were included in this study.

Patients belonging to age group 20-50 years of both the sexes were included.

It is a prospective double blind randomized controlled study. The study was approved by the Ethical Committee and were randomly grouped into three groups.

Group A (Esmolol 0.5 mg/kg) = Twenty patients were given Esmolol 0.5 mg/kg IV 2 minutes before intubation.

Group B (Esmolol 1.0 mg/kg) = Twenty patients were given Esmolol 1 mg/kg IV 2 minutes before intubation.

Group C (Esmolol 1.5 mg/kg) = Twenty patients were given Esmolol 1.5 mg/kg IV 2 minutes before intubation.

The surgeon was also duly informed of the study.

The study was done during the period from May 2009 to August 2009 in the Department of Anaesthesiology, Chengalpattu Medical College, Chengalpattu.

Inclusion Criteria :	ASA I & II
	Age 20 – 50 yrs
	All cases requiring GA
Exclusion criteria :	Known and difficult airways
	Esmolol contraindications
	Not meeting inclusion criteria
	Patients on beta blockers
	Patients with full stomach
	Patients posted for Emergency surgery
	Hypertension, Diabetes, Ischemic heart disease

Randomization was done by draw of lots. The follow up of the patient and analysis of data were done by personnel blinded to which group belonged to. Drawing of lots for randomization and preparation of study was prepared by a consultant who took no further part in the study, the rest of the study was conducted by investigator who was blinded to the drug injected.

MATERIALS

1. Inj.Thiopentone Sodium 2.5%

2. Inj. Succinylcholine Chloride

3. Inj. Glycopyrrolate

4. Inj. Fentanyl citrate

5. Inj. Esmolol HCl 100mg/10 ml

6. Disposable 20 ml syringe

7. Laryngoscope with blades 3 and 4

8. Endotracheal tubes of varying sizes.

9. Emergency drugs

10. Difficult Intubation strategies

PRE OPERATIVE PREPARATION

All the patients were admitted and they underwent relevant investigations. Preoperatively informed, written consent was obtained from the patient.

Hemogram, Bleeding time, Clotting time

Blood – urea

sugar

Serum – creatinine

electrolytes

X ray Chest

Electrocardiogram

Other relevant investigations were obtained on the basis of the condition of the patient.

ANAESTHESIA PROTOCOL

Pre operative visit was done to allay anxiety and good rapport was established with the patient.

All the patients were given pre operative night sedation with tablet Diazepam 10 mg and antacid prophylaxis with tablet Ranitidine 150 mg orally.

INTERVENTION

Induction of anaesthesia was standardized for all the patients.

PREMEDICATION

All the patients were premedicated with Injection. Glycopyrrolate 4 μg/kg body weight, intra muscularly, 45 minutes before surgery. Basal pulse rate and blood pressure were recorded.

MONITORING

Non Invasive Automated BP

Electrocardiogram

Pulseoximetry

ETCO2

Patient shifted to operating table after 45 minutes. In the operating room patients were connected to baseline monitors, then intravenous access established with 18 gauge cannula and intravenous fluids started. Pulse rate, Blood pressure, ECG and SpO2 were recorded.

PREOXYGENATION

Preoxygenation was done with 100% oxygen for 3 minutes.

ADMINISTRATION OF STUDY DRUG

Inj. Fentanyl 2µg/kg iv given three minute prior to induction. The study drug was taken in a 20 ml syringe and diluted to 20 ml and given as bolus over 15-20 seconds two minutes before intubation. One minute later anaesthesia was induced with 2.5% Inj. Thiopentone sodium 5mg/kg IV. and Inj. Succinyl choline 1.5mg/kg IV given. After satisfying muscle relaxation, the patient was intubated with appropriate size endotracheal tube after doing a proper laryngoscopy within 10-15 seconds. Conditions were prolongation of laryngoscopy time due to difficult intubation, these patients were excluded from the study. Endotracheal tube was secured after confirming bilateral air entry. Anaesthesia maintained with N2O & O2 (66.7%: 33.3%) and IPPV was done. The ETCO2 was maintained at the of pressure of 30-35 mmHg.

The whole intra operative & post operative period were uneventful.

STATISTICAL ANALYSIS

Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure. All recorded data were entered using MS Excel software and analysed using STATA software for determining the statistical significance. **ANOVA test** was used to determine the significance among three groups. **Student's t test** was used to compare the two groups on mean values of various parameters. **The p-value taken for significance is <0.05.**

LIST OF SURGICAL PROCEDURES

S. No.	Surgery	Group A	Group B	Group C
1.	Herniorraphy	5	5	5
2.	Fibroadenoma excision	4	3	3
3.	Pyelolithotomy	3		1
4.	FESS	3	4	2
5.	Thyroidectomy	2	3	2
6.	Appendicectomy	1		1
7.	Screw fixation& Plating	2	2	1
8.	Gynaecomastia- excision		1	
9.	Hydrocele eversion		1	
10.	Parotidectomy		1	3
11.	Cholecystectomy			2

OBSERVATION AND RESULTS

Sixty patients under this study were categorized into three groups. They comprised of both sexes with age ranging from 20-50 years.

The age, sex and body mass index were equal in all the three groups. P value was not significant in the study done ($p>0.05$).

DEMOGRPHIC PROFILE

AGE

GROUP	20-30	31-40	41-50	TOTAL
A	9	3	8	20
B	8	6	6	20
C	9	4	7	20
TOTAL	26	13	21	60

SEX

GROUP	MALE	FEMALE	TOTAL
A	8	12	20
B	10	10	20
C	9	11	20
TOTAL	27	33	60

MEAN AGE AND BMI OF PATIENTS BY GROUPS

AGE

GROUP	AGE	BMI
A	35.9±8.6	21.5±1.4
B	35.1±8.7	21.6±1.4
C	34.9±8.4	22±1.5
P-value	**>0.05**	**>0.05**

BMI

GROUP	19-24	>24	TOTAL
A	19	1	20
B	19	1	20
C	18	2	20
TOTAL	56	4	60

At intake of study, there is no significance difference on age and BMI of patients among the groups.

The Groups are:

Group A (Esmolol 0.5 mg/kg): Twenty patients were given Esmolol 0.5mg/kg IV 2 minutes before intubation as a bolus.

Group B (Esmolol 1.0 mg/kg): Twenty patients were given Esmolol 1mg/kg IV 2 minutes before intubation as a bolus.

Group C (Esmolol 1.5 mg/kg): Twenty patients were given Esmolol 1.5mg/kg IV 2 minutes before intubation as a bolus.

Heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were measured before premedication, after premedication, during administration of the study drug, during induction, during intubation, after intubation and following for about 7 minutes after laryngoscopy and intubation for every minute.

Table I, II, III and IV shows the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure comparisons between the three groups.

HEART RATE

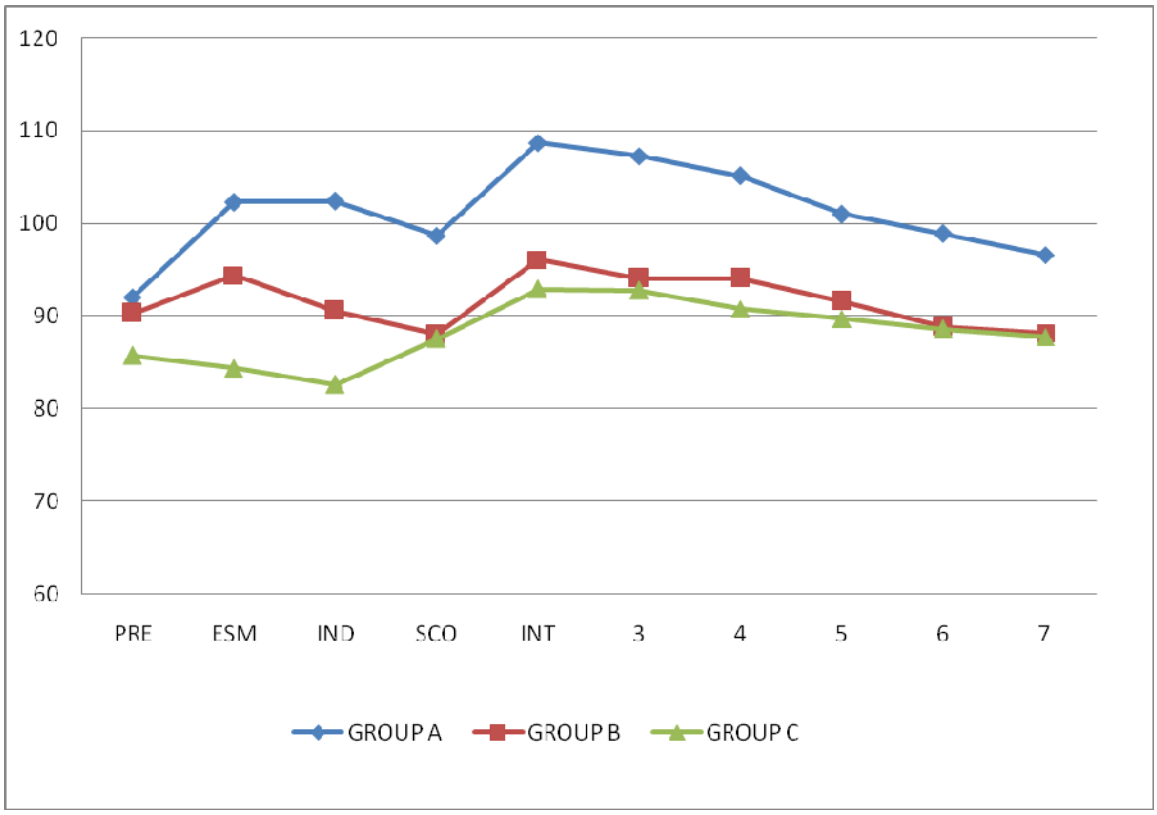

120
110
100
90
80
70
60
PRE
ESM
IND
SCO
INT
3
4
5
6
7
GROUP A
GROUP B
GROUP C

TABLE-1

DISTRIBUTION OF MEAN ± STANDARD DEVIATION OF HEART RATE BY GROUPS

HEART RATE MEAN±SD VALUES				P value
TIME	GROUPS			
	A	B	C	
PRE MED	92.1 ± 8.1[80-110]	90.3 0± 5.2[83-102]	90.3±3.4[86-102]	>0.05
ESMOLOL	102.3 ±7.4[92-118]	94.40 ±2.6[91-99]	92.8±3.9[88-101]	<0.0001
AT INDUCTION	102.4 ±6.6[94-116]	90.55± 3.8[83-97]	89.4±3.9[84-98]	<0.0001
AFTER SCOLINE	98.7± 6.8[90-115]	88.1 ±3.3[80-93]	87.60 ±6.5[77-103]	<0.0001
AT INTUBATION	108.7± 6.3[100-124]	96.1 ±3.6[92-102]	92.90 ±6.4[83-108]	<0.0001
AT 3 MIN	107.3 ±5.9[100-122]	94.10 ±4.0[85-100]	92.80± 6.4[83-108]	<0.0001
AT 4 MIN	105.1±6.0[98-120]	94.10 ±4.2[85-100]	90.8± 6.3[81-105]	<0.0001
AT 5 MIN	101 .0±5.9[95-116]	91.55± 4.3[83-98]	89.7± 6.5[80-105]	<0.0001
AT 6 MIN	98.9 ±5.9[92-114]	89.85 ±4.3[81-97]	88.6 ± 6.6[78-104]	<0.0001
AT 7 MIN	96.6± 5.9[90-111]	88.15 ±4.4[79-96]	87.75 ±6.3[78-103]	<0.0001

SYSTOLIC BLOOD PRESSURE

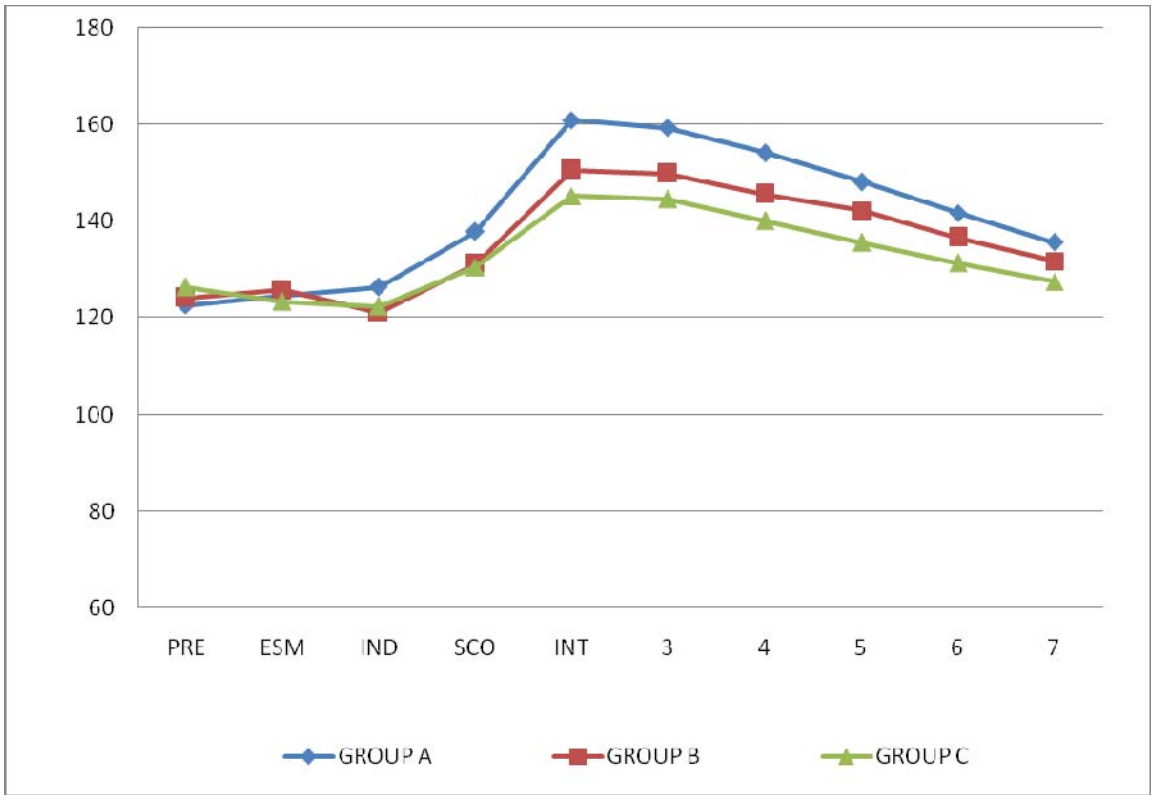


TABLE –II

DISTRIBUTION OF MEAN ± STANDARD DEVIATION OF SYSTOLIC BLOOD PRESSURE BY GROUPS

SYSTOLIC BLOOD PRESSURE	MEAN ± SD VALUES			P VALUE
TIME	GROUPS			
	A	B	C	
PRE MED	122.6 ±6.5[110-132]	124.05± 5.8[110-131]	126.2± 5.7[111-136]	>0.05
ESMOLOL	124.6± 6.26[111-132]	125.65± 6.3[112-135]	123.4 ±6.0[108-134]	>0.05
AT INDUCTION	126.4± 6.6[113-138]	120.95± 5.8[108-129]	122.4 ±6.6[106-130]	<0.05
AFTER SCOLINE	137.8±6.4[125-146]	131.1±5.89[118-140]	130.5 ±6.3[114-138]	<0.05
AT INTUBATION	160.9±7.7[145-171]	150.5± 5.7[138-161]	145.15± 5.3[131-153]	<0.0001
AT 3 MIN	159.2±7.6[148-170]	149.8± 5.3[138-160]	144.6 ±4.9[131-153]	<0.0001
AT 4 MIN	154.1± 6.8[140-166]	145.5± 5.2[135-156]	139.9±4.8[127-148]	<0.0001
AT 5 MIN	148.1±6.5[135-160]	142.2 ± 5.4[132-154]	135.6 ±4.6[123-144]	<0.0001
AT 6 MIN	141.7 ± 6.48[130-152]	136.5± 5.4[128-148]	131.3 ±4.6[119-140]	<0.0001
AT 7 MIN	135.6±6.3[125-146]	131.7± 5.4[123-143]	127.5 ±4.3[117-135]	=0.0001

DIASTOLIC BLOOD PRESSURE

TABLE-III

DISTRIBUTION OF MEAN ± STANDARD DEVIATION OF DIASTOLIC BLOOD PRESSURE BY GROUPS

DIASTOLIC BLOOD PRESSURE	MEAN ± SD VALUES			P VALUE
TIME	GROUPS			
	A	B	C	
PRE MED	82.3± 5.9[71-90]	82.6 ±5.5[71-90]	84.55 ±6.1[71-92]	>0.05
ESMOLOL	83.7±6.3[72-92]	84 ±5.0[73-92]	82.35 ±5.9[68-90]	>0.05
AT INDUCTION	85.5±6.3[70-96]	80.2± 5.6[68-89]	81.55±5[68-90]	<0.05
AFTER SCOLINE	92.9±5.3[84-101]	86.2 ±4.3[76-96]	87.3±5.1[76-96]	<0.0001
AT INTUBATION	105.1± 5.2[98-116]	98.2 ±4.4[90-106]	95.35±4[88-104]	<0.0001
AT 3 MIN	103.4±4.98[98-113]	97.2 ±4.13[89-104]	95.1±3.6[88-101]	<0.0001
AT 4 MIN	99.6±4.0[93-108]	93.95±4.1[86-101]	91.2± 4.1[81-98]	<0.0001
AT 5 MIN	95.3±4.6[89-104]	90.65± 4.1[82-98]	88.05±3.9[79-95]	<0.0001
AT 6 MIN	91±3.27[86-98]	87.5 ±4.3[80-94]	84.9±3.5[76-90]	<0.0001
AT 7 MIN	87.8±3.7[81-96]	84.4 ±4.1[76-92]	82±3.5[74-88]	<0.0001

MEAN ARTERIAL PRESSURE

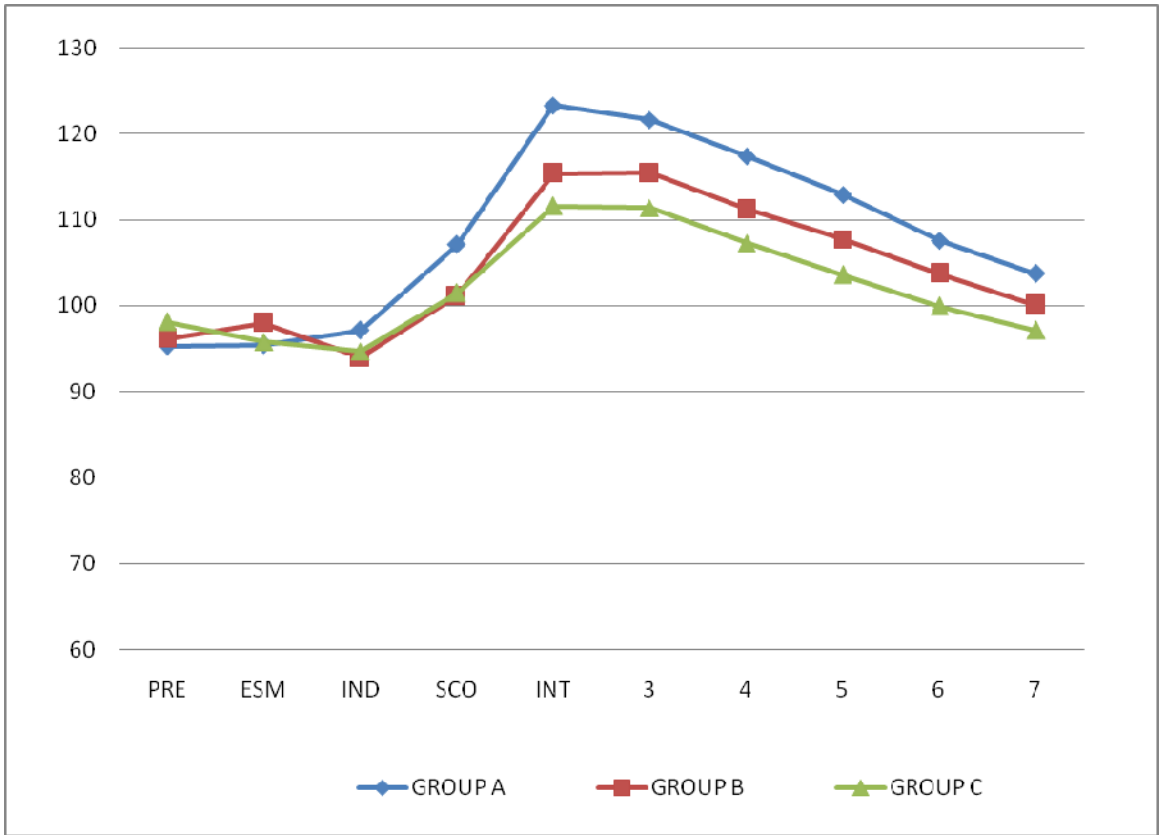


TABLE-IV

DISTRIBUTION OF MEAN ± STANDARD DEVIATION OF MEAN ARTERIAL PRESSURE BY GROUPS

MEAN ARTERIAL PRESSURE	MEAN±SD VALUES			P VALUE
TIME	GROUPS			
	A	B	C	
PRE MED	95.3±6.0[84-103]	96.1±5.1[84-103]	98.1±5.3[85-106]	>0.05
ESMOLOL	95.4±6.2[84-102]	98±4.9[86-106]	95.7±5.7[81-103]	>0.05
AT INDUCTION	97.1±6.7[84-110]	94±5.5[84-102]	94.7±5.6[80-103]	>0.05
AFTER SCOLINE	107.1±5.8[96-115]	101.1±4.9[90-110]	101.5±5.0[91-110]	<0.05
AT INTUBATION	123.3±5.8[113-134]	115.4±4.8[106-126]	111.6±4.3[102-120]	<0.0001
AT 3 MIN	121.6± 5.6[115-132]	115.4±4.6[106-125]	111.4±4.4[102-120]	<0.0001
AT 4 MIN	117.4±4.3[110-125]	111.15±4.4[102-119]	107.3±4.7[96-118]	<0.0001
AT 5 MIN	112.8±4.9[106-121]	107.6±4.60[99-118]	103.5±4.0[93-110]	<0.0001
AT 6 MIN	107.5±3.6[101-114]	103.6±4.6[96-112]	99.9±3.7[90-106]	<0.0001
AT 7 MIN	103.6± 4.1[96-112]	100.1±3.7[94-107]	97.1±3.6[88-104]	<0.0001

GROUP A: (Esmolol 0.5mg/kg)

Heart Rate:

The increase in heart rate following laryngoscopy and intubation was up to 18%. The rise in heart rate was highest during intubation and following intubation and it was high till the sixth minute after intubation. It started declining only at the seventh minute.

No rhythm disturbances were observed.

Systolic Blood Pressure:

There was up to 31% increase in systolic blood pressure during the study period. Highest value attained during intubation and following intubation. It started declining only after the study period.

Diastolic Blood Pressure:

Changes in blood pressure were similar to changes in systolic blood pressure. There was a 27% rise in diastolic pressure from the baseline during the procedure. It was highest during and following intubation. It started declining by 10 mmHg at the end of fifth minute.

Mean Arterial Pressure:

The mean arterial pressure rise was up to 29% from the baseline during the period of study. It was maximum during and following

intubation. It started declining by 10 mmHg at the fifth minute. There was a further decline of about 8 mmHg at the end of the study.

Group B (Esmolol 1.0 mg/kg)

Heart rate:

The rise in heart rate was about 12% in this group during the whole study period. There was a initial decline in heart rate of about 5 per minute following Esmolol. The maximum heart rate was observed following intubation. It started declining at the fifth minute and there was further decline to baseline values at the seventh minute.

No rhythm disturbances were observed.

Systolic blood pressure:

There was a 24% rise in systolic blood pressure from the baseline during the study period. The highest value recorded was during and following intubation. It started declining at the end of seventh minute.

Diastolic blood pressure:

Changes in blood pressure were similar to changes in systolic blood pressure. There was a 22% rise in diastolic pressure from the baseline during the procedure. It was highest during and following intubation. It started declining to baseline values at the end of seventh minute.

Mean arterial pressure:

There was a 22% rise in mean arterial pressure from the baseline during the procedure. It was highest during and following intubation. There was a decline in mean arterial pressure at fifth minute.

Group C (Esmolol 1.5 mg/kg)

Heart rate:

There was only about 5% rise in heart rate from the baseline values during the entire study period. The maximum rise was observed during intubation and at one minute following intubation. The rise was modest of about 2-3 beats per minute. It started declining to baseline values at fourth minute. There was a further decline in heart rate from the baseline values at sixth and seventh minute.

No rhythm disturbances were observed.

Systolic blood pressure:

The rise in systolic blood pressure was about 18% during the entire study period. The maximum values were observed during intubation. It started declining following intubation. At the seventh minute it reached the baseline values.

Diastolic blood pressure:

There was an initial decline in diastolic blood pressure following Esmolol and during induction from the baseline. There was a rise of about 16% during and following intubation. It started declining at the fifth minute and reached baseline value at sixth minute. It further decline below baseline at seventh minute.

Comparison of variables on the three groups

Variables	**Group A**	**Group B**	**Group C**
Heart Rate	18%	12%	5%
Systolic Blood Pressure	31%	24%	18%
Diastolic Blood Pressure	27%	22%	17%
Mean Arterial Pressure	29%	22%	17%

Heart rate and rhythm:

In Group A, the rise in heart rate was about 18% from the baseline values during and following intubation and it took longer time to reach the baseline values. There was a rise of about 16 beats per minute from baseline following laryngoscopy and intubation.

In Group B, there was an initial fall in heart rate following bolus dose of Esmolol and there was a rise of about 8 beats per minute

following laryngoscopy and intubation. The rise in heart rate was about 12% from the baseline following laryngoscopy and intubation. It returned back to baseline value at the sixth minute.

In Group C the rise in heart rate was modest of about 2-3 beats per minute and the values returned to baseline values at the fourth minute. The rise was 5% from the baseline values with least fluctuation in heart rate during the study period. There was a decline in heart rate at fourth minute and a further decline was observed at sixth and seventh minute from the baseline values.

There is **no statistical significance** among the mean value of heart rate at the pre-medication time($p > 0.05$). But it is **significantly different** during administration of Esmolol bolus, induction, intubation during and for about seven minutes following laryngoscopy and intubation. It was significantly lower in Group C than in Groups A and B ($p < 0.001$). The initial fall in Group B is because of its direct action on cardiac conducting system.

There was no record of arrhythmias in any of the patients in any of the group. This is probably because of all the patients are of ASA Class I and II with no history of hypertension or no other cardiac ailments.

Blood Pressure:

Systolic blood pressure:

There is **no statistical significance** on mean value among the three groups at Pre-Medication and during administration of Esmolol bolus ($p>0.05$).

But, it is **statistically significant** on all other period of study ($p<0.001$) in between the three groups.

There is 31%, 24% and 18% increase from base line during the operation in group A, group B and group C respectively. The rise in the systolic blood pressure is comparatively less in Group C from the Groups A and B.

Higher mean value reached at intubation in all 3 groups.

Diastolic blood pressure:

There is **no statistical significance** on mean of Diastolic Blood Pressure at Pre-Medication and Esmolol ($p>0.05$). But, it is **statistically significant** during induction ($p<0.05$). It is also **statistically significant** from the period of intubation to the end of study period($p<0.001$)..

. There is up to 27%, 22% and 17% increase from base line during the operation in group A , group B and group C respectively.

Higher mean value reached at intubation in all the groups.

Mean arterial pressure:

There is **no statistical significance** on mean value of MAP up to Induction during the period of study ($p>0.05$). But it is **statistically significant** after the induction till the end of the study period ($p<0.001$).

There is up to 29%, 22% and 17% increase from base line during the operation in group A, group B and group C respectively.

Higher mean value reached at intubation in all 3 groups.

DISCUSSION

Laryngoscopy and intubation produces hemo dynamic stress response characterized by hypertension and tachycardia. This neuro endocrine response causes a variety of complications in patients with cardiac disease due to imbalance between myocardial oxygen supply and demand like ST changes, ventricular arrhythmias and pulmonary oedema.

This is also hazardous in patients with vascular pathologies that cause weakening of the lining of the major arteries in particular cerebral and aortic aneurysms. In patients with hydrocephalus or intra cranial mass lesions the increase in cerebro spinal fluid pressure may produce transient impairment of cerebral perfusion.

Direct laryngoscopy[3] that does not exceed 15 seconds duration is helpful in minimizing the blood pressure elevation evoked by this painful stimulus.

In view of the frequent occurrence of hypertension and tachycardia during laryngoscopy even in the normotensive individual, it is perhaps rather surprising that complications have not been met very often. Reason for this may be the transient nature of the hypertension which usually lasts for less than ten minutes. It is possible however that some of the complications that occur during intubation or even later in the course of

anaesthesia may be precipitated by an episode of hypertension and tachycardia following endo tracheal intubation.

This reflex response may be diminished or modified locally, centrally or peripherally and attempts have been made to accomplish this with varying success by different techniques and agents. No effective drug has been found out so far to abolish this response.

Ebert TJ and Bernstein JS (1990)[6] studied that hemodynamic response to Rapid sequence induction and intubation in healthy patients with a single bolus dose of Esmolol. They concluded that Esmolol 2 mg/kg bolus effectively attenuated heart rate, systolic blood pressure, diastolic blood pressure increases produced by laryngoscopy and intubation. In our study also we took 2 minute as the time for administering Esmolol prior to laryngoscopy and intubation.

Sheppard et al[7] (1990) compared different bolus dose of Esmolol and concluded that attenuation of intubation response is adequate following 100 mg of Esmolol.

Helfman SM et al[9] (1991) compared the efficacy of Lidocaine , Fentanyl, Esmolol to obtund the intubation responses and concluded that only Esmolol provided constant and reliable part against increase in heart rate and systolic blood pressure accompanying laryngoscopy and intubation.

Miller D.R et al (1991)[10] in their Canadian multicentre trial involving 548 patients concluded that 100 mg bolus Esmolol is safe and effective agent. This dose of Esmolol combined with low dose of Fentanyl (2-3mcg/kg) results in effective control of both heart rate and blood pressure while avoiding important side effect.

Ganbatz C.L et al [11](1991) also had similar results of Miller D.R et al.,

Vucovic M et al[12] (1992) studied about the use of Esmolol for management of cardiovascular responses to laryngoscopy and tracheal intubation and found that pressor response to laryngoscopy was significantly less marked in patients given Esmolol 2 minutes before intubation which was similar to our timing of drug administration.

Vucovic M et al[12] (1992) concluded randomized control trial with 500 mcg/kg/min for 2 minutes and maintenance 100 mcg/kg/min till intubation and showed that heart rate , systolic blood pressure were significantly decreased in Esmolol group.

Kovac et al (1992)[14] concluded that in an eye patient with coronary artery disease, or in any patient whom increase in heart rate may be detrimental, Esmolol may be a useful adjunct in combination with low dose alfentanil to attenuate the increase in heart rate due to laryngoscopy and intubation.

Yuan L,Chia YY (1994)[15] studied the efficiency of bolus dose Esmolol in blunting the stress response comparing 100 mg Esmolol versus 200 mg Esmolol. They concluded that both bolus dose of Esmolol could effectively attenuate the increase the heart rate, hypertension produced by laryngoscopy and intubation, furthermore, Esmolol 200 mg presented a better hemodynamic stability than100 mg Esmolol. In our study Esmolol 1.5 mg/kg provided better hemodynamic control than Esmolol 1mg/kg bolus.

Sharma S, Ghania A (1995)[16] also concluded adequate hemodynamic control was obtained with the administration of Esmolol bolus 2mg/kg.

Weist D et al (1995)[17] made a review of therapeutic efficacy and pharmacokinetic characteristics of Esmolol.

Singh H et al (1995)[18] in their study concluded that Lidocaine 1.5 mg/kg IV and Nitroglycerine 2 mcg/kg IV were effective in controlling the acute hemodynamic response following laryngoscopy and intubation. Esmolol 1.4 mg/kg was significantly more effect than either Lidocaine or Nitroglycerine in controlling heart rate or mean arterial pressure increase during intubation.

Sharma et al[19] (1996) compared the ability of different bolus doses of Esmolol to blunt the hemodynamic response to laryngoscopy and intubation in treated hypertensive patients. Concluded that Esmolol 100mg given as bolus is effective as well as safe in blunting the response.

In our study it was Esmolol 1.5 mg/kg IV bolus was effective and safe in blunting the response.

Feng C.K et al [20](1996) concluded that Esmolol only could reliably offer protection against increase in both heart rate and systolic blood pressure. Low dose Fentanyl (2 mcg/kg) prevented heart rate but not increase in heart rate and 2 mg/kg lidocaine had no effect.

Wang L et al[22](1999) concluded that 1.2 mg/kg bolus of Esmolol is effective and safe. We also used Esmolol in the range of 0.5 mg/kg to 1.5 mg/kg, which was also safe.

Bensky et al (2000)[24] in their study concluded that small dose of Esmolol may block the increase in heart rate and blood pressure resulting from laryngoscopy and intubation.

Figueredo, E.Garcia- Fuentes EM (2001)[25] compared the results of 38 randomized control trial involving different regimen and doses of Esmolol and found that the most effective regimen was a loading dose of 500 mcg/kg/min over 4 minute, followed by continuous infusion dose of 200-300 mcg/kg/min.

Analysis of the length of our study showed that Esmolol 1.5 mg/kg was more effective in attenuating the heart rate response to laryngoscopy and intubation.

Also, Esmolol 1.5 mg/kg was effective in attenuating the blood pressure increase accompanying laryngoscopy and intubation.

CONCLUSION

On taking into consideration the criteria which I chose to study the hemo dynamic changes expected, I found that the dose of Esmolol 1.5 mg/kg (Group C) to be effective in attenuating the hemo dynamic responses during laryngoscopy and endo tracheal intubation with no major adverse effects of Esmolol.

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PROFORMA

Name: Age/ Sex: IP no: Ht:

Wt:

Clinical Diagnosis: Surgery:

Investigations

Hb	PCV	BT	CT	ECG	CXR	RFT

Monitors

ECG	NIBP	SpO2	ETCO2

Premedication: Preoxygenation:

Induction: Maintenance:

Esmolol Dose:

TIME	After pre-med	At esmolol	Induction	At scoline	At intubation (2 min)	At 3 min	At 4 min	At 5 min	At 6 min	At 7 min
Heart rate										
Blood pressure (Systolic)										
Blood pressure (Diastolic)										
Mean Arterial Pressure										

Group-A

S.No	Wt	Age	Sex	I.P.No	BMI	AT PREMED				AT ESMOLOL				AT INDUCTION				AFTER SCOLINE				AT INTUBATION				AT 3 MIN				AT 4 MIN				AT 5 MIN				AT 6 MIN				AT 7 MIN			
						HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP
A1	48	29	2	16846	22.8	91	117	74	88	100	118	74	88	101	113	70	84	98	125	85	96	106	151	104	119	105	149	104	119	103	140	98	112	100	135	95	108	98	132	94	106	96	130	90	103
A2	52	43	1	12462	20.8	80	130	88	102	92	128	90	102	94	128	90	101	90	142	98	112	102	171	115	133	100	170	113	132	98	158	108	124	95	155	104	121	93	148	98	114	91	145	96	112
A3	48	45	2	15205	21.8	85	132	88	102	96	132	86	101	95	130	86	100	91	145	98	113	100	168	110	129	101	168	110	129	99	154	106	122	95	151	104	121	92	145	96	112	90	142	94	110
A4	49	26	2	11067	20.4	105	112	72	85	110	114	74	84	109	120	78	92	106	130	86	101	114	151	101	117	112	151	101	117	110	148	98	114	106	145	95	116	104	131	92	105	102	128	88	101
A5	58	45	1	12670	22.6	85	128	86	100	96	127	89	101	97	126	86	93	94	140	95	110	104	168	108	128	102	165	104	124	100	156	100	118	95	151	96	114	93	146	91	109	91	138	89	105
A6	50	33	2	13854	19.5	98	121	84	96	108	125	84	96	108	125	88	94	106	135	94	107	115	158	104	122	113	155	101	117	110	149	98	115	106	141	94	109	104	141	89	106	102	135	86	104
A7	48	22	2	10385	20.4	110	110	71	84	118	111	72	84	116	115	75	84	115	128	85	96	124	145	98	113	122	155	98	117	120	154	96	115	116	146	91	109	114	139	88	105	111	130	88	102
A8	55	40	2	11669	22	90	121	84	96	102	126	85	96	102	126	86	101	100	134	96	107	110	156	105	122	108	154	100	118	106	148	96	113	104	143	92	109	102	140	88	105	99	135	86	102
A9	48	26	2	13147	20.8	98	112	73	85	110	115	73	84	108	120	80	93	103	131	87	102	115	160	99	119	113	148	98	115	111	144	93	110	106	139	89	106	103	130	86	101	100	125	81	96
A10	48	45	2	13905	20.1	88	128	84	98	100	129	88	101	101	135	90	105	96	142	94	108	108	165	103	123	108	163	101	121	106	160	100	120	101	148	94	112	99	141	90	107	97	130	84	99
A11	58	45	2	15036	22.6	85	129	85	98	96	128	86	96	97	134	90	105	92	143	94	109	102	165	104	123	102	164	104	124	100	161	102	119	97	149	96	113	95	140	91	106	93	128	86	100
A12	50	30	2	15666	20.8	99	116	76	89	110	118	78	91	107	120	80	93	101	132	84	100	105	150	101	117	103	151	101	117	100	148	98	115	96	143	94	110	94	138	90	105	92	135	90	105
A13	48	29	2	15757	20.2	100	120	81	94	110	121	82	95	111	125	84	96	105	133	88	103	115	155	101	119	114	150	98	115	112	148	96	113	108	142	92	108	106	136	88	104	104	130	84	99
A14	50	30	2	16493	20	102	124	84	96	113	128	84	96	114	126	85	96	110	140	91	107	119	160	99	119	117	158	98	118	115	156	97	116	110	150	94	112	108	144	90	108	106	136	88	104
A15	58	37	1	21026	22.6	87	121	84	96	98	126	85	96	98	125	88	94	94	136	93	107	105	156	101	119	103	155	99	117	101	154	97	116	97	148	91	110	95	142	88	106	93	135	84	101
A16	52	25	1	16485	20.3	90	126	88	100	101	130	90	101	100	128	88	95	96	140	96	108	108	165	108	127	105	158	105	122	102	154	99	117	97	148	90	109	95	140	90	106	92	135	85	101
A17	54	47	1	18782	24.5	85	130	90	103	96	132	92	102	98	138	96	110	94	145	100	115	105	170	116	134	103	170	112	131	100	165	106	125	96	160	102	121	94	152	96	114	91	146	94	111
A18	56	45	1	17259	23.6	88	128	88	101	98	131	91	102	99	137	95	104	95	146	101	115	105	168	112	130	105	170	112	131	103	166	106	125	99	158	103	120	97	152	95	114	95	145	90	108
A19	56	30	1	11436	22.4	90	121	81	95	98	125	84	96	97	128	88	101	95	145	98	113	107	168	109	128	106	166	107	126	103	161	101	121	98	157	98	117	96	151	92	111	94	143	88	106
A20	54	45	1	10519	21.6	85	126	86	98	94	128	88	97	96	128	88	101	93	144	96	112	104	167	105	125	104	164	102	122	102	158	98	118	98	152	92	112	95	146	88	107	93	140	86	104

Group-B

S.No	Wt	Age	Sex	I.P.No	BMI	AT PREMED				AT ESMOLOL				AT INDUCTION				AFTER SCOLINE				AT INTUBATION				AT 3 MIN				AT 4 MIN				AT 5 MIN				AT 6 MIN				AT 7 MIN			
						HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP
B1	54	45	1	13365	22.6	85	128	84	98	95	130	86	100	87	125	84	98	92	135	90	105	102	154	104	120	100	151	101	120	100	146	95	112	98	143	93	109	97	138	88	104	95	135	85	103
B2	55	40	1	13716	21.4	90	125	84	97	94	128	86	98	90	122	83	97	85	132	88	102	97	152	104	120	93	150	104	120	93	145	98	113	91	142	90	109	91	137	87	103	88	132	84	100
B3	60	38	1	10820	24	85	124	85	98	93	120	81	96	84	118	78	90	90	128	86	100	100	148	100	113	90	148	98	115	90	144	96	112	88	140	93	108	86	135	90	105	84	130	85	100
B4	58	44	1	11461	21.4	88	130	90	103	96	129	90	102	90	125	86	99	85	135	90	105	92	155	101	119	94	154	101	119	93	150	98	115	91	147	96	111	89	142	94	110	87	137	91	106
B5	55	30	1	10933	21.2	91	125	85	97	92	128	88	98	93	123	83	97	88	133	85	105	96	156	100	118	97	155	100	118	98	152	100	118	94	148	98	118	92	142	94	110	90	138	92	106
B6	50	26	1	14756	22.2	90	125	85	97	99	128	86	98	92	124	84	97	87	132	84	100	96	155	99	118	99	155	98	119	99	151	96	117	93	147	94	111	91	142	92	109	90	137	88	105
B7	60	35	1	13419	22.2	85	124	86	98	95	121	81	96	83	119	79	96	93	129	87	101	99	149	98	115	85	148	97	115	85	144	95	111	83	141	93	109	81	136	88	103	79	130	85	101
B8	45	27	2	10246	19.6	100	118	76	90	97	120	78	92	91	116	76	89	91	126	84	98	102	145	94	111	93	145	94	111	94	140	90	106	90	137	86	103	88	130	81	97	86	126	78	95
B9	45	20	2	14885	20.5	102	112	72	85	92	116	76	89	93	108	70	84	88	118	76	90	96	138	90	106	95	139	89	106	95	135	86	102	93	133	84	100	91	128	80	96	89	123	76	94
B10	48	35	2	18627	21	96	121	84	97	91	120	81	96	97	121	81	96	92	131	88	102	97	149	96	113	100	148	96	113	99	145	93	110	97	140	90	108	95	135	88	103	93	130	85	100
B11	68	42	1	13509	25.1	83	131	88	102	91	135	92	106	85	129	89	102	80	140	96	110	90	161	106	126	88	160	104	125	88	156	101	119	83	154	98	116	81	148	94	112	80	143	90	107
B12	50	27	1	18884	19.5	88	126	86	98	93	124	81	97	90	120	78	92	85	131	86	101	95	151	97	115	92	151	96	115	93	146	92	110	88	142	89	106	87	137	88	103	86	132	84	99
B13	50	30	2	10521	22.2	94	118	72	90	94	120	78	96	96	115	70	85	91	125	81	95	98	144	90	108	98	144	90	108	99	140	86	104	97	135	82	99	95	130	80	97	94	126	78	95
B14	51	50	2	12008	22.3	90	128	88	98	91	134	90	105	90	126	84	97	85	136	89	104	92	156	96	116	93	155	94	115	94	150	91	110	94	148	88	108	92	143	84	103	90	138	82	100
B15	50	26	2	11648	19.2	96	110	71	84	96	112	73	86	96	108	68	84	91	118	78	90	97	138	94	108	99	138	94	108	100	135	91	105	98	132	88	102	96	128	85	97	96	123	85	97
B16	50	48	2	13362	22.2	91	130	85	102	96	135	86	102	92	128	83	99	87	138	88	104	93	152	96	114	96	151	95	114	96	148	93	111	94	145	91	109	92	130	88	102	90	126	86	98
B17	48	35	2	13711	21.3	92	124	85	98	91	128	86	100	94	122	83	87	89	132	88	102	99	152	104	120	94	150	103	120	94	144	98	113	92	141	89	106	90	137	87	103	88	131	84	99
B18	55	25	1	14774	21.4	84	126	81	97	95	129	87	101	88	121	81	96	90	133	85	101	99	153	96	115	90	153	96	115	90	149	92	111	88	146	90	108	86	141	91	108	85	136	86	102
B19	49	35	2	15165	21.7	88	125	84	97	98	128	86	100	90	121	81	96	85	132	87	102	91	151	101	117	93	150	98	116	92	146	94	112	91	142	90	106	89	136	85	104	87	131	84	98
B20	50	45	2	15179	21.9	88	131	81	97	98	128	88	102	90	128	84	99	86	138	88	104	92	151	98	115	93	150	96	116	90	145	94	112	88	141	91	107	88	136	86	104	86	130	81	97

Group-C

S.No	Wt	Age	Sex	I.P.No	BMI	AT PREMED				AT ESMOLOL				AT INDUCTION				AFTER SCOLINE				AT INTUBATION				AT 3 MIN				AT 4 MIN				AT 5 MIN				AT 6 MIN				AT 7 MIN			
						HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP
C1	45	36	2	18760	22.7	91	126	86	99	89	122	84	96	88	122	84	96	93	130	88	102	98	145	98	113	99	144	98	113	97	139	93	108	95	135	90	105	95	130	86	100	94	126	84	98
C2	50	45	2	17102	21.9	92	130	92	104	88	127	88	101	87	127	86	100	92	135	92	106	96	140	94	109	96	140	94	109	94	135	90	105	93	131	86	101	91	127	84	98	90	123	81	95
C3	50	45	2	16136	21.5	89	131	88	102	88	127	86	99	96	127	87	99	90	135	94	107	97	148	98	114	97	147	97	114	95	142	94	110	94	138	91	106	93	134	89	104	92	130	87	101
C4	45	30	2	18181	20	92	125	84	98	91	123	81	95	89	123	80	95	94	130	85	100	100	145	94	111	99	144	94	111	97	139	91	107	96	135	89	104	95	130	86	100	94	126	84	98
C5	50	22	2	10385	22.2	102	115	71	85	100	110	70	83	98	106	68	82	103	116	76	91	108	131	88	102	108	131	88	102	105	127	81	96	105	123	79	93	104	119	76	90	103	117	74	88
C6	50	30	2	12875	20.7	88	128	78	94	93	124	76	92	84	123	75	91	89	131	81	97	94	146	96	112	94	145	97	112	92	140	93	108	91	135	89	104	90	131	86	101	88	128	83	98
C7	48	45	2	13362	21	90	130	82	98	101	128	82	97	94	126	81	96	86	134	88	103	91	149	93	110	91	147	93	110	89	142	91	108	87	137	88	104	87	132	86	101	86	128	83	98
C8	52	45	2	13909	20.7	91	129	87	101	92	127	84	98	90	125	81	96	85	131	83	99	90	145	91	109	90	144	92	108	88	139	90	106	86	135	88	103	86	131	84	99	85	127	81	96
C9	60	22	1	10388	21.5	90	121	84	96	93	120	80	93	92	116	78	91	80	125	82	96	85	140	91	107	85	140	90	106	83	135	85	101	82	131	82	98	80	127	81	96	80	124	78	93
C10	50	29	1	12029	20	86	126	88	99	96	124	84	97	93	123	81	95	82	131	86	101	87	146	95	112	87	145	94	111	85	140	90	106	84	136	86	102	84	131	82	98	84	127	80	95
C11	60	35	1	11268	21.5	92	128	88	99	92	126	86	99	90	126	85	98	77	134	87	102	84	148	97	114	84	148	97	114	82	143	93	109	80	138	90	106	78	133	86	101	78	129	84	99
C12	55	37	2	16275	22.5	88	125	81	97	100	121	81	94	84	121	81	94	90	129	86	100	95	141	94	109	95	141	94	109	93	137	90	105	92	134	88	103	91	130	83	98	90	126	80	95
C13	50	28	2	16100	22.2	90	111	71	86	93	108	68	81	86	106	76	80	91	114	82	92	96	138	90	106	96	138	89	106	94	135	86	102	92	131	83	99	89	127	81	96	88	123	76	94
C14	48	30	2	16680	20.8	90	121	81	94	92	120	78	92	86	121	78	91	91	129	86	100	96	144	94	110	96	145	95	110	94	140	89	106	95	135	86	102	94	130	83	98	93	127	81	96
C15	60	45	1	10688	23.4	86	136	91	106	88	134	88	103	85	130	86	101	79	138	94	108	85	152	104	120	84	151	101	120	82	146	98	114	81	141	95	110	80	137	90	105	80	135	88	104
C16	58	39	1	20723	22.6	89	129	88	101	91	126	87	99	92	124	84	97	86	132	90	104	90	150	98	115	90	148	98	115	88	143	94	110	87	138	91	106	86	135	88	103	85	130	85	100
C17	60	42	1	22441	23.4	91	131	88	101	90	128	86	100	89	130	86	99	83	138	94	108	88	152	101	118	88	151	100	118	86	148	98	118	85	144	93	110	85	140	90	106	84	135	86	102
C18	60	30	1	21238	25	88	128	90	102	95	124	88	100	87	121	83	96	92	131	89	103	97	146	96	112	96	146	96	112	94	141	92	108	93	137	88	104	92	132	85	100	90	128	81	96
C19	55	21	1	24400	20.2	88	125	81	97	92	121	80	94	86	121	81	94	91	129	87	101	98	144	94	110	98	144	94	110	96	140	90	106	95	135	86	102	94	131	83	99	93	126	80	95
C20	58	42	1	25455	25.7	87	130	92	102	91	128	90	102	91	130	90	103	78	138	96	110	83	153	101	118	83	153	101	118	81	148	96	113	80	143	93	109	78	139	89	105	78	135	84	101