Dissertation on

ATTENUATION OF HEMODYNAMIC RESPONSES TO TRACHEAL EXTUBATION : COMPARISON OF DILTIAZEM, LIGNOCAINE AND DILTIAZEM-LIGNOCAINE COMBINATION.

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CERTIFICATE

This is to certify that the Dissertation "**ATTENUATION OF HEMODYNAMIC RESPONSES TO TRACHEAL EXTUBATION: COMPARISON OF DILTIAZEM, LIGNOCAINE AND DILTIAZEM-LIGNOCAINE COMBINATION**" is the original work done by **Dr.M.K.NARASIMHAN** in the Department of Anaesthesiology, Madras Medical College and Government General Hospital, Chennai for the award of Degree of M.D. (Branch X) Anaesthesiology, during the academic period of 2004-2007.

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This is to certify that the Dissertation "**ATTENUATION OF HEMODYNAMIC RESPONSES TO TRACHEAL EXTUBATION: COMPARISON OF DILTIAZEM, LIGNOCAINE AND DILTIAZEM-LIGNOCAINE COMBINATION**" presented herein by **Dr.M.K.NARASIMHAN** is an original work done in the Department of Anaesthesiology, Madras Medical College and Government General Hospital, Chennai for the award of Degree of M.D. (Branch X) Anaesthesiology under my guidance and supervision during the academic period of 2004-2007.

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DECLARATION

I hereby declare that dissertation entitled "**ATTENUATION OF HEMODYNAMIC RESPONSES TO TRACHEAL EXTUBATION: COMPARISON OF DILTIAZEM, LIGNOCAINE AND DILTIAZEM-LIGNOCAINE COMBINATION**", has been the original work done by me, under the guidance of **PROF.DR.G.SIVARAJAN, M.D., D.A** Professor and Head of Department of Anaesthesiology, Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. (Anaesthesiology) examination to be held in March 2007.

This study was conducted at Madras Medical College and Government General Hospital, Chennai.

I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Place : Chennai. **DR.M.K.NARASIMHAN**
Date :

CONTENTS

INTRODUCTION

Tracheal intubation as well as extubation often provoke significant cardiovascular changes with marked increase in heart rate and blood pressure[1-3]. These hemodynamic changes during extubation are probably of little consequence in healthy individuals but may be more severe and more dangerous in hypertensive patients[4]. Hemodynamic changes during extubation and emergence from anaesthesia may cause dangerous increase in myocardial oxygen demand in patients with coronary artery disease and in those with risk factors for CAD[4,5]. Several drugs like lignocaine, esmolol, alfentanil, fentanyl, prostaglandin E_1 and diltiazem are used to attenuate the cardiovascular responses to tracheal extubation in normotensive patients[6-10].

Diltiazem a calcium channel blocker has been used extensively to maintain perioperative hemodynamic stability[11,12]. This drug is effective in blunting the hemodynamic changes associated with laryngoscopy and tracheal intubation[13]. The exact mechanism whereby tracheal intubation and extubation cause hemodynamic changes may be different and remain as yet to be elucidated.

Tracheal intubation produces a profound but short uniform stimulation in the anaesthetized patient. But during tracheal extubation stimulation which affects the

hemodynamic changes is multifactorial; e.g., pain of the wound, emergence from anaesthesia and tracheal irritation. Even if a drug is used effectively to control cardiovascular changes during tracheal intubation, its dose and timing of dosing most probably are different during extubation.

Because the pharmacological mechanism for the control of the hemodynamic changes during extubation is thought to differ between diltiazem and lignocaine, combining these two drugs may be more effective than giving each drug alone for attenuating cardiovascular responses. The present study was undertaken to compare the efficacy of diltiazem along with lignocaine with each drug given alone in suppressing the hemodynamic changes during extubation in normotensive patients.

After getting approval from the hospital ethical committee, the study was carried out in the Department of Anaesthesiology, Madras Medical College and Government General Hospital, Chennai.

AIM OF THE STUDY

The aim of the study is to evaluate the efficacy of combination of diltiazem with lignocaine in suppressing the hemodynamic changes during tracheal extubation and to compare the effects with these drugs given individually.

TRACHEAL EXTUBATION

Extubation of the trachea is the Cinderella of anaesthetic practice. Although it seems that there are more problems associated with extubation than intubation the world wide incidence is not known. A recent review[4] concluded that extubation is associated with much short-term morbidity and occasionally mortality.

The common problems associated with tracheal extubation are

1. **Physiological responses to tracheal extubation:**

Dyson and colleagues[7] recorded increases of 20% or more in both heart rates and systolic arterial pressures in about 70% of normal patients who were extubated under standard conditions. This response was increased in hypertensive, cardiac and neuro surgical patients. The response in pre-eclamptic patients can also be very severe, culminating in pulmonary edema and death.

2. **Trauma:**

Trauma to any of the structures forming the upper and lower airway is possible during tracheal extubation.

3. **Airway obstruction:**

Airway obstruction following tracheal extubation is commonly due to –

A : Laryngospasm

B : Laryngeal oedema

C : Vocal cord paralysis

D : Tracheal collapse.

A:Laryngospasm:

Defined as an occlusion of the glottis by the action of intrinsic laryngeal muscles. Laryngospasm is the most common cause of upper airway obstruction after tracheal extubation. It is particularly frequent in children after upper airway surgery and is most likely to occur after tracheal extubation of a patient in lighter planes of anaesthesia. The main treatment is administration of 100% oxygen with continuous positive airway pressure. Intravenous doxapram, lignocaine, diazepam and suxamethonium chloride followed by reintubation and ventilation have all been used in the treatment of laryngospasm.

B:Laryngeal edema:

It is an important cause of upper airway obstruction after extubation in children particularly neonates and infants. Oedema may be localized to supraglottic, subglottic

or retro arythenoid regions. In a study by Koka et al factors that showed a positive correlation with the development of laryngeal edema in children included the use of a tight fitting endotracheal tube, trauma during intubation and duration of intubation. The presence of upper airway infection was not a significant contributory factor.[14]

C:Vocal cord paralysis:

Rare but important cause of airway obstruction. It results from trauma to the vagus nerve or its branches and is described after surgical procedures involving the head and neck, the thyroid gland or thoracic cavity. It has been suggested that tracheal intubation itself may result in nerve damage leading onto vocal cord palsy. The recurrent laryngeal nerve after leaving the thorax travel in the tracheo- oesophageal groove towards the larynx where they divide into anterior and posterior branches. The anterior branch has been found to be susceptible to compression by the tracheal tube cuff where they lie beneath the muscle and immediately medial to the lamina of the thyroid cartilage.

D:Tracheal Collapse:

May result from prolonged compression by an expanding goitre or tumour particularly within the confines of the thoracic inlet. Tracheal collapse occurs after extubation and requires emergency reintubation. The subsequent options include surgical resection of the affected segment or airway diversion below the affected trachea through a tracheostomy.

4. **Pulmonary edema associated with upper airway obstruction:**

This usually occurs within minutes of development of upper airway obstruction or after relief of obstruction. The pathogenesis is multifactorial, but the markedly negative intrathoracic pressure generated during an episode of acute upper airway obstruction is the dominant mechanism. Resolution occurs spontaneously over a period of hours. Essentials of management include maintenance of airway, administration of oxygen and positive pressure ventilation if required.

5. **Pulmonary aspiration of gastric contents**:

Can occur if the patients are not fully conscious and able to protect their airway.

6. **Post operative sore throat**:

Cuffs with a longer cuff–trachea interface appear to cause a higher incidence of sore throat [15]. The incidence of sore throat may also be related to intracuff pressures. One study demonstrated that tube size is related to the incidence and severity of sore throat in both sexes[16].

7. **Difficulty in extubation:**

This could be due to inability to deflate the tracheal cuff, a large cuff catching onto the vocal cords or the endotracheal tube getting transfixed by a suture or a wire to an adjacent structure.

PHYSIOLOGICAL RESPONSES TO EXTUBATION

CARDIOVASCULAR EFFECTS:

Many investigators have documented that tracheal extubation causes modest (10-30%) and transient increases in blood pressure and heart rate lasting 5-15 min[17-19]. Coriat et al demonstrated that patients with coronary artery disease experience significant decrease in ejection fraction (from 55% $\pm$ 7% to 45% $\pm$ 7%) after extubation[20]. The changes in ejection fraction occurred in the absence of ECG signs of myocardial ischemia. Wellwood et al reported that patients with a cardiac index of less than 3.0 L/min/m^2 did demonstrate an ischemic response to stress of postoperative tracheal extubation after myocardial re vascularisation[21]. These patients experienced decrease in myocardial lactate extraction, LV compliance and cardiac performance.

Tracheal extubation after cesarean section in parturients with gestational hypertension can cause significant increase of 45 and 20mm Hg in mean arterial and pulmonary artery pressures respectively. It was concluded that tracheal extubation and related hemodynamics increased the risk of cerebral hemorrhage and pulmonary edema in them [22].

In hypertensive patients, emergence from anaesthesia and tracheal extubation is associated with significant increase in heart rate and blood pressure. Fuji et all studied the cardiovascular responses to tracheal extubation or LMA removal in normotensive and hypertensive patients[23]. They concluded that hemodynamic variables immediately following extubation or LMA removal from baseline values were greater in hypertensive patients than in normotensives. Hypertensive patients thus exhibit an exaggerated response to tracheal extubation when compared to normotensive patients.

Coughing often occurs during tracheal extubation. Coughing can lead to increase in intrathoracic pressure, which can interfere with venous return to the heart. In a study by Kern et al [24] coughing significantly increased systolic pressure (from 137$\pm$ 25 to 176 $\pm$ 30 mm Hg), diastolic pressure (71$\pm$ 10 to 84 $\pm$ 18 mm Hg) and arterial pulse pressure (from 65 $\pm$ 27 to 92 $\pm$ 35 mm Hg) without changing heart rate. Mean coronary flow velocity decreased (from 17 $\pm$ 10 to 14 $\pm$ 12 cm/s) in these patients.

In summary significant hemodynamic stimulation to varying degrees can be transiently produced by tracheal extubation. Although these changes are usually inconsequential patients at particular risk may be adversely affected by tracheal extubation. Thus the potential for deletrious hemodyamic events to follow extubation should not be ignored.

Neurologic effects of extubation:

Laryngoscopy and intubation increases intracranial pressure the greatest increase being elicited in patients with decreased intracranial compliance[25]. However the effects of tracheal extubation on ICP have not been investigated. Although it is likely that extubation causes transient increases in ICP, the existence of such effects must be extrapolated from other data.

Donegan and Bedford[26] reported that ICP increased by 12 $\pm$ 5 mm Hg in comatose patients whose tracheas were suctioned. White et al[27] also found ICP increased from 15 $\pm$ 1 to 22 $\pm$ 3 mm Hg after endotracheal suctioning in fully resuscitated comatose intensive care unit patients. The ICP increases lasted for less than 3 min after suctioning. Both authors hypothesized that coughing associated with endotracheal suctioning causes ICP to rise by increasing intrathoracic pressure, cerebral venous pressure and cerebral blood volume.

Increases in arterial blood pressure often result from tracheal extubation as mentioned above and arterial hypertension can also lead to or be associated with intracranial hemorrhage or increase in ICP[28]. Possibly, associated hemodynamic changes, during and after extubation can also negatively impact patients with intracranial pathology.

In summary coughing, bucking and arterial hypertension during tracheal extubation can all be detrimental especially in patients with existing intracranial pathology.

Hormonal effects of extubation;

Recognition that a significant and potentially deleterious stress response can result from the induction of anaesthesia, tracheal intubation and surgery has led to numerous documentations of this phenomenon. On the other hand, the endocrine response to tracheal extubation has received little attention. Lowrie et al[19] evaluated the impact of tracheal extubation on changes in plasma concentrations of epinephrine and norepinephrine in patients undergoing major elective surgery. Epinephrine levels were significantly increased only 5 min after extubation. Norepinephrine levels remained unchanged.

Adams et al[29] performed an investigation in which 40 patients, undergoing herniorrhaphy or cholecystectomy, were anaesthetized with either isoflurane or halothane and extubated at 0.5 MAC depth of anaesthesia or awake. Significant increase in plasma epinephrine levels occurred in all patients. Norepinephrine levels also increased in all patients except those extubated awake after halothane anaesthesia. Although antidiuretic hormone levels increased in all patients after extubation, neither adrenocorticotrophic hormone nor cortisol levels did. These investigations indicate that an endocrine response to tracheal extubation can occur.

PHARMACOLOGY OF LIGNOCAINE

Lignocaine is an amide local anaesthetic with antiarrhythmic properties. Lofgren first noted that all local anaesthetics have a hydrophilic portion (secondary or tertiary amine) and a lipophilic portion (aromatic residue) separated by an intermediate chain. Linkage to the aromatic residue has provided a means for classification of local anaesthetics. Local anaesthetics with an ester linkage between the aromatic residue and intermediate chain are **AMINOESTERS** (procaine, chloroprocaine and tetracaine) and those with an amide linkage between the aromatic residue and intermediate chain are **AMINOAMIDES** (lignocaine, bupivacaine, mepivacaine etc,)

It belongs to the class Ib of the Vaughan Williams classification of antiarrhytmic drugs. Lignocaine blocks the fast sodium channels in the cell membranes of myocardial cells and reduces the rate of rise of the action potential in the His purkinje system and the ventricular musculature. The duration of the action potential and effective refractory period are reduced. The sinoatrial node and atrio-ventricular node are not affected by therapeutic concentrations of lignocaine.

Pharmacokinetics:

The pharmacokinteics of lignocaine is well described by a two compartment model following a single intravenous dose. Its distribution half life (t ½ ∝) is around 8 minutes and its elimination half life (t ½ β) is around 90 to 110 minutes. Lignocaine is metabolized in the liver to monoethylglycinexylidine (MEGX) and glycinexylidine (GX) which are then excreted by the kidney. As lignocaine is rapidly cleared by the liver its plasma steady state concentration depends on the hepatic blood flow. Thus in conditions where hepatic blood flow is reduced as in congestive cardiac failure or in the presence of hepatic disease the dosage of lignocaine should be reduced. Lignocaine has a molecular weight of 234. Its protein binding is between 60-75% Therapeutic plasma concentrations required to produce an antiarrhytmic effect is around 1.5μg/ml. Convulsion occurs at a plasma concentration of around 10 μg/ml.

Indications:

1. Intravenous lignocaine is the drug of choice for management of ventricular arrhytmias like ventricular premature contractions.

2. Intravenous lignocaine is used during anaesthesia to prevent the pressor response to laryngoscopy and intubation.

3. Lignocaine is used as a local anaesthetic for topical infiltration and other regional anaesthetic procedures.

It is available as 1%, 2%, 4% and 10% solutions. A 5% solution with 7.5% dextrose is available for subarachnoid block. The preparations for intravenous use do not contain preservatives. Usual dose for intravenous administration is 1-1.5mg/kg body weight followed by an infusion at a rate of 1-4 mg/min if required. For infiltration lignocaine can be used up to a maximum dose of 3mg/kg body weight without adrenaline and 7mg/Kg body weight with adrenaline.

Contraindications:

1. Hypersensitivity to lignocaine.
2. Hypersensitivity to other amide local anaesthetics.

Precautions

1. Patients with hepatic or renal dysfunction:

Lignocaine is mainly metabolised in the liver and the metabolites are execreted by the kidney. Caution should be observed while administering lignocaine to patients with these disorders especially as infusion as it may lead on to an accumulation of metabolites potentiating toxicity.

2. When high doses are used in patients with impaired myocardial function it can potentiate the negative inotropic effect and cause clinical hypotension.

3. Serum potassium levels should be normalized prior to starting an infusion of lignocaine.

Toxicity:

Toxicity of local anaesthetics chiefly involves the central nervous system and cardiovascular system. The earliest symptoms in an awake patient include circumoral paraesthesias and numbness, which then proceeds onto tinnitus, nystagmus and dizziness. Further increase in plasma concentration can lead onto CNS excitation restlessness and tremors leading onto convulsions. Local anaesthetics cause peripheral vasodilation and myocardial depression. At toxic doses the combined effects of peripheral vasodilation, negative inotropic effect and a depressant action on cardiac conduction can lead onto circulatory collapse and cardiac arrest.

The ratio of the dosage or blood levels required to produce irreversible cardiovascular collapse to the dosage or blood levels required to elicit convulsions is the CC/CNS ratio. The CC/CNS ratio for lignocaine in adult non-pregnant sheep is 7 indicating that 7 times as much drug is needed to produce irreversible cardiovascular collapse as is required to produce convulsions. Hence central nervous system symptoms provide a warning in an awake patient of high plasma levels and impending cardio vascular collapse

Management of Toxicity:

1. Administer oxygen, intubate if necessary.

2. Seizures are managed by intravenous benzodiazepines or thiopentone sodium.

3. Cardio vascular depression is managed by intravenous fluid administration and vasopressors. Prolonged inotropic support may be required.

4. Hypoxia and acidosis worsen cardiovascular collapse and should be aggressively managed.

CALCIUM CHANNEL BLOCKERS

Drugs that are classified as calcium channel blockers act selectively on specialized membrane channels inhibiting the inward movement of calcium ions into cardiac and smooth muscle cells. In contrast to skeletal muscle, which contains adequate stores of calcium ions, cardiac and vascular smooth muscle are dependent on extra cellular calcium for their contractile function.

The entry of calcium ions into the cells occur through specific gates or membrane channels that can be opened or closed. Some of them are opened by stimulation of nearby adrenergic receptors (receptor operated channels) while others are opened by depolarization of the cell membrane (Voltage activated channels). These calcium ion conductance channels are sometimes referred to as 'Slow Channels' in contrast to the 'Fast Channels' that conduct sodium. The various voltage gated calcium ion channels include.

Voltage sensitive calcium channels

S.No.		L - Type (Long lasting current)	T – Type (Transient current)	N – Type (Neuronal)

01.	Conductance	25 ps.	8 ps.	12-20ps.
02.	Activation threshold	High	Low	High
03.	Inactivation rate	Slow	Fast	Medium

S.No.		**L - Type (Long lasting current)**	**T – Type (Transient current)**	**N – Type (Neuronal)**
04.	Location and function	Excitation – contraction – coupling in cardiac and smooth muscle . SA, AV mode – conductivity – Endocrine cells – hormone release – neurons – transmitter release.	SAnode – pacemaker activity. T current and repetitive spikes in thalamic and other neurons. Endocrine cells – hormone release. Certain arteries constriction.	Only on neurons in CNS, sympathetic & myentric plexuses – transmitter release.
05.	Blocker	Nifedipine, diltiazem, verapamil.	Mebefradil, flumarizine, ethosuximide.	ω-conotoxin.

Most of the commercially available calcium channel blocking agents exclusively block the L– Channels.

Role of calcium ions in cardiac and smooth muscle cells.

The cardiac action potential can be divided into five phases.

Phase O: **Rapid Depolarisation:** This is due to the opening of fast sodium channels and a rapid influx of sodium ions.

Phase 1 : **Early Repolarisation:** Here the sodium channels close but the membrane conductance for calcium and potassium ions increase. The overall effect is a small change of the membrane potential towards the resting membrane potential.

Phase 2: **Plateau :** This is due to an increase in membrane conductance to calcium ions.

Phase 3: **Rapid repolarisation:** There is reduction in the inward movement of calcium ions and potassium ion efflux.

Phase 4: In non – pacemaker cells this phase is characterized by a constant membrane potential. In pacemaker cells there is a slow diastolic depolarization which brings the membrane potential near the threshold potential.

Thus calcium ions are responsible for the Phase 1 and Phase 2 of the action potential in cardiac cells. But in specialized cells like pace maker cells and conducting tissue Phase O occurs as a result of slow calcium influx.

In smooth muscle cells:

The inward flux of calcium ions produces additional release of calcium from the intracellular storage sites. This calcium then binds to calmodulin, a calcium binding protein. The calcium-calmodulin complex activates myosin light chain kinase, which phosphorylates myosin. This results in actin-myosin interaction leading onto muscle contraction.

In cardiac muscle:

Calcium ions bind on to the protein troponin. This results in the release of inhibition of troponin on the interaction between action and myosin. Actin myosin interaction leads onto muscle contraction.

Thus calcium ions play an important role in coupling the depolarization of myocardial and smooth muscle cells to muscle contraction. Excitation contraction coupling.

Commercially available calcium channel blockers can be classified on the basis of their chemical structure into

1. PHENYLALKYLAMINES - Verapamil
2. BENZOTHIAZEPINES - Diltiazem
3. DIHYDROPYRIDINES - Nifedipine.

All voltage sensitive calcium channels are membrane spanning funnel shaped glycoproteins that function as ion selective valves. They are composed of major α_1 subunit which encloses the ion channel and other modulatory subunits like α_2, β, δ. In L-type Ca^{2+} channels each subunit exists in multiple isoforms, which may be site specific.

Skeletal muscle L – Channels -α_{IS}, $\alpha_2/\delta a$, β_1 -γ

Cardiac muscle L – Channels - α_{Ica}, $\alpha_2/\delta c$, β_2

Smooth muscle L – Channels - α_{Icb}, α_2/δ, β_3

All these drugs prevent calcium ion entry into cardiac and smooth muscle cells by blocking the α_1 subunit of L type voltage gated calcium channels. They differ in their tissue selectivity and mechanism of blockade. Dihydropyridines are more selective for arteriolar beds while phenylalkylamines and benzothiazepines are selective for the atrioventricular node.

Common indications for calcium channel blockers :

1. **Angina Pectoris**: Calcium channel blockers have been used in the management of stable and vasospastic angina. The mechanisms by which they are thought to play a beneficial effect in angina include.

a) increased myocardial oxygen supply due to coronary artery dilatation and an increase in coronary blood flow.

b) decreased myocardial oxygen demand due to decrease in peripheral vascular resistance, myocardial contractility and heart rate.

2. **Hypertension:** Calcium channel blockers by virtue of their peripheral vasodilation have been used in the management of systemic arterial hypertension.

3. **Supraventricular arrhytmias**: Verapamil and Diltiazem have been used for the management of supraventricular arrhytmias. Both these drugs prolong the refractory period of the atrio-ventricular node. This is one of the main mechanism by which nodal supraventricular arrhytmias are abolished and the rate in atrial flutter and fibrillation controlled. These drugs have been used in the conversion of paroxysmal supraventricular tachycardia to sinus rhythm as well as controlling the rapid ventricular rate in atrial fibrillation.

Other indications of calcium channel blockers:

1. Cerebral vasospasm accompanying subarachnoid hemorrhage:

Nimodipine which selectively dilates the cerebral arteries has been widely used in the management of cerebral vasospasm.

2. Cerebral protection after global ischemia:

Calcium channel blockers by virtue of blocking the calcium ion influx has been studied for cerebral protection following induced or accidental cardiac arrest.

3. Hypertrophic cardiomyopathy.

4. Adjunct to cold cardioplegia.

5. Primary pulmonary hypertension.

6. During harvest of radial artery grafts in coronary artery bypass surgery:

Dilitiazem has been used as an infusion to prevent vasospasm of radial

artery grafts intraoperatively and during the immediate post operative period in patients undergoing coronary artery bypass surgeries.

7. Preterm labour: Oral nifedipine has been used in preterm labour as a tocolytic.

8. Calcium channel blockers have been used in vasospastic conditions like Raynand's disease.

9. Non-specific calcium channel blockers like cinnarizine have been used in the management of migraine.

Comparative properties of calcium channel blockers

S.No.		Verapamil	Nifedipine	Diltiazem
01.	Channel blocking potency	++	+++	+
02.	Frequency dependence of channel blockade.	++	-	+
03.	Channel recovery rate.	Much delayed	No effect	Less delayed
04.	Cardiac effects: heart rate	↓	↑	↓
	A-V conduction velocity.	↓↓	-	↓
	Contractility	-, ↓	↑	↓
	Output	-, ↓	↑	-, ↑
05.	Vascular smooth muscle relaxation	++	+++	+
06.	Clinical use in	Angina Arrhythmia	Angina Hypertension	Angina, Hypertension

		Hypertension	Congestive heart failure	Arrhythmia.

Diltiazem

Diltiazem hydrochloride predominantly blocks the calcium channels in the atrioventricular node.

The pharmacological effects include –

- Decrease in myocardial contractility
- Decrease in heart rate.
- Decrease in rate of conduction through the AV node.
- Dilation of vascular smooth muscle resulting in decreased blood pressure.

The effects of diltiazem on the sinoatrial node, atrioventricular node and its vasodilating properties appear to be intermediate between verapamil and nifedipine.

Pharmacokinetics:

Following oral administration over 90% is absorbed but bioavailability is around 40-45% due to first pass hepatic metabolism. Onset of action is between 15-30 min with a peak at 1-2 hours. Elimination half-life is 4-6 hours. Protein binding is

around 80-85%. The therapeutic plasma concentration is around 100-250 ng/ml. Diltiazem is metabolized in the liver by acetylation. Unlike verapamil and nifedipine only 35% is excreted through the kidneys, the remaining being eliminated by the liver. It is available as 30mg, 60 mg and 90mg tablets and 120 mg sustained release tablets. Patients are started on 30 mg four times daily and increased to a maximum of 180 – 240 mg per day.

The intravenous preparation is a clear, colourless solution with pH between 2.7-4.1. Following a single intravenous injection it appears to obey linear pharmacokinetics over a dose range of 10.5 – 21 mg. The onset of action after a single intravenous bolus dose is between 30 sec. and 1min. with the peak effect at 2-5 minutes. Its apparent volume of distribution is around 305 litres. The high volume of distribution is due to its lipid solubility.

It is available as 5ml vials with each vial containing 25mg of diltiazem hydrochloride (5mg/ml). The intravenous dose is 75-150 μg/Kg.

Contraindications

1. Patients with sinus bradycardia, sick sinus syndrome, second or third degree AV block.
2. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome.
3. Patients receiving intravenous beta adrenergic blockers should not be administered intravenous diltiazem concomitantly.
4. As there are no well-controlled studies in pregnant women, diltiazem should be used during pregnancy only if the potential benefit to the mother justifies the

potential risk to the fetus.

5. Patients with known hypersensitivity to the drug.

Adverse Effects

1. Hypotension: Hypotension can occur which usually responds to intravenous normal saline or placing the patient in Trendelenberg position.

2. Bradycardia, junctional rhythm and high degree AV block can occur especially in patients with pre-existing nodal disease.

3. Other side effects include headache, dizziness, ankle edema and constipation particularly with the oral medication.

4. Elevation of liver enzymes has also been reported.

ANAESTHETIC IMPLICATIONS

i) Interaction with Volatile anaesthetics:

Calcium channel blockers are vasodilators and myocardial depressants. The negative inotropic effects, depressant effects on sinoatrial node function and peripheral vasodilating effect of these drugs and those of volatile anaesthetics are similar and there is evidence that volatile anaesthetics have blocking effects on calcium channels. Enflurane when combined with calcium channel blockers produces more myocardial depression than halothane.

ii) Neuromuscular blocking drugs:

Calcium channel blockers potentiate the effects of depolarizing and non-depolarizing neuromuscular blocking drugs. This potentiation resembles that produced by mycin antibiotics. The postulated mechanisms include presynaptic alterations, reducing calcium concentration, blocking of sodium channels etc. The local anaesthetic effect of verapamil may also contribute to potentiation of neuromuscular blocking drugs.

iii) Potassium containing solution:

Calcium channel blockers slow the inward movement of potassium ions. Hyperkalemia can occur in patients being treated with calcium channel blockers after much smaller amounts of exogenous potassium infusion as associated with use of KCl to treat hypokalemia or administration of stored whole blood.

iv) Dantrolene:

The administration of dantrolene in the presence of verapamil or diltiazem results in hyperkalemia and cardiovascular collapse. Whenever calcium channel blockers and dantrolene are to be administered concurrently invasive hemodynamic monitoring and frequent measurement of plasma potassium concentration are recommended.

v) Digoxin:

Calcium channel blockers may increase the plasma concentration of digoxin presumably by decreasing its plasma clearance.

vi) Platelet function:

Calcium channel blockers may interfere with calcium medicated platelet functions.

REID AND BRUCE (1940) postulated that reflex circulatory responses to laryngeal instrumentation were mediated through the vagus nerve and they named it as **"Vaso Vagal Reflex".**

WYCOFF.C.C.(1960)[30] in his study stated that topical anaesthesia of the pharynx along with superior laryngeal nerve blocks reduced the increase in mean arterial pressure after intubation.

STEINHAUS & GASKIN (1963)[31] found that intravenous lignocaine suppressed the cough reflex.

MASON & ECKANKOFF (1971) proved that the hypertensive response in patients can be significantly decreased by simple lignocaine spray.

PRYS ROBERTS et al (1971) found that the increase in heart rate and blood pressure are much more exaggerated in hypertensive patients.

DENLIGNER.J.K. and ELLISON.N.E. (1974)[33] have used intratracheal lignocaine spray which causes a 50% reduction in the hypertensive response.

BIDWAI AV & STANLEY TH (1978)[17] demonstrated that tracheal

administration of 1.5cc of 4% Lignocaine 3 to 5 min prior & 1cc of 4% lignocaine at extubation prevented increase in heart rate and blood pressure during tracheal extubation.

BIDWAI AV & BIDWAI VA (1979)[6] demonstrated that intravenous administration of lignocaine 2mg/kg body weight 2min prior to extubation prevented increase in heart rate and blood pressure.

DYSON A(1990)[7] in his study found that esmolol when given as a single intravenous bolus dose of 1.5mg/kg body weight 2 to 5 minutes before extubation attenuates the cardiovascular responses to tracheal extubation.

MUZZI et al(1990)[48] in his study compared labetolol and esmolol in the control of hypertension after intracranial surgery and found that the incidence of bradycardia in the immediate postoperative period was significantly higher with labetolol.

FUHRMAN et al (1992)[8] compared the efficacy of alfentanil a short acting opioid with esmolol a short acting beta adrenergic blocker in attenuating the hemodynamic changes during extubation. They found that esmolol was superior to alfentanil in attenuating the hemodynamic changes when given as bolus dose at discontinuation of anaesthesia.

NISHINA et al (1995)[9] studied the effects of fentanyl in blunting the hemodynamic responses to tracheal extubation. They studied 60 females undergoing

elective gynaecological surgeries and who randomly received saline, 1μg/kg body weight fentanyl, 2μg/kg body weight fentanyl intravenously at the time of peritoneal closure. It was demonstrated that cardiovascular changes during tracheal extubation were attenuated by a single dose of fentanyl (2μg/kg). But such techniques can produce depression of respiratory and cardiovascular systems and may also result in difficulty in management of airway.

NISHINA et al (1995)[50] studied the attenuation of the cardiovascular changes during tracheal extubation with diltiazem (0.1mg/kg and 0.2 mg/kg body weight) and compared it with lignocaine 1mg/kg body weight. They found that a bolus of diltiazem 0.2mg/kg body weight had the greatest inhibitory effect while the extent of attenuation with diltiazem 0.1mg/kg was similar to lignocaine 1mg/kg body weight.

NISHINA K and MIKAWA K(1996)[10] in their study found that prostaglandin E_1 in a dose of 0.1μg/kg/min infusion started at the end of surgery and continued until 5 minutes after extubation attenuated the hypertensive response to tracheal extubation but failed to blunt the tachycardia associated with tracheal extubation.

MIKAWA et al(1996)[49] studied the effect of intravenous verapamil (0.05mg/kg and 0.1 mg/kg) body weight on the cardiovascular changes during tracheal extubation and compared the same with diltiazem (0.2mg/kg body weight). They concluded that both calcium channel blockers attenuated the cardiovascular responses and this effect was greatest with verapamil 0.1mg/kg body weight.

FUJII et al(1998)[51] studied the inhibitory effect of nicardipine 30μg/Kg body weight on the hemodynamic effects of tracheal extubation in hypertensive patients and compared it with diltiazem 0.2mg/kg body weight. They concluded that diltiazem when compared to nicardpine produces greater attenuation of circulatory responses to tracheal extubation in the hypertensive population.

YUHJI SAITOH & YOSHITAKA FUJI (1999) [44] did a randomized double blind study to evaluate the efficacy of combination of diltiazem and lignocaine in suppressing the hemodynamic changes during tracheal extubation in hypertensive patients undergoing elective orthopedic surgery. They concluded that the combination of diltiazem and lignocaine is more effective prophylaxis than diltiazem or lignocaine alone for attenuating the cardiovascular responses to tracheal extubation and emergence from anaesthesia in hypertensive patients.

MATERIALS AND METHODS

The study was done to compare the efficacy of combined diltiazem and lignocaine with that of giving each of these drugs separately in suppressing the hemodynamic changes during tracheal extubation in patients posted for elective spine surgeries (lumbar & cervical spine). The study comprised of 60 patients of both sex in the age group of 16 to 60 years. All the patients were informed of the study and prior written informed consent was obtained. The surgeon was also informed about the study.

Patients were assessed by a detailed history & physical examination supported by investigations like routine blood tests – Hb, blood sugar, blood urea, serum creatinine, serum electrolytes, chest X-ray PA view and Electrocardiogram.

INCLUSION CRITERIA

1) Patients in ASA Physical Status I & II.
2) Age 16 to 60 years.
3) Patients with modified Mallampatti scores I & II.

EXCLUSION CRITERIA

1) Patients with predicted difficult airway.
2) Patients with co-existing cardio vascular diseases (Hypertension, conduction blocks , Ischaemic heart diease & cardiac failure).
3) Patients on cardiovascular drugs (β-blockers, Calcium channel blockers).

4) Patients with heart rate < 60 beats / min. (hypothyroidism, sinus node disease, other medications).

5) Patients with blood pressure less than 100/60mm Hg.

6) Patients with documented hepatic or renal disease.

7) Pregnant patients.

ANAESTHESIA PROTOCOL

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

PREMEDICATION:

All the patients were given Tab-Diazepam 10 mg. orally the night before surgery. Tab-Ranitidine 150mg and T-Metoclopromide 10mg were given one and half-hours before surgery. All the patients were given Inj. Atropine 20µg/kg body weight intramuscularly 45 minutes before surgery.

MONITORING

After receiving the patient in the operating room the heart rate and arterial oxygen saturation of all patients were monitored continuously . The heart rate was monitored by electrocardiography (lead II) while the blood pressure was recorded using an automated non-invasive blood pressure monitor. An intravenous cannula was inserted after infiltration with local anaesthetic.

INDUCTION AND INTUBATION:

All patients were pre oxygenated for 3 min. and anaesthesia induced with intravenous administration of Thiopentone (5mg/kg) and Fentanyl citrate (2µg/Kg). Tracheal intubation was facilitated by intravenous administration of Vecuronium bromide (0.1mg/Kg). Anaesthesia maintained with Isoflurane (0.5-1%) and Nitrous oxide (66%) in O_2. Supplemental doses of Fentanyl and Vecuronium were administered when required.

Patients were randomly allocated to one of the three groups before the end of surgery.

Group L - 1.5mg/Kg body weight of Lignocaine + Saline.

Group D - 0.1mg/Kg body weight of Diltiazem + Saline.

Group D-L - 0.1mg/Kg body weight of Diltiazem +
1.5mg/Kg body weight of Lignocaine.

Identical syringes containing each drug were prepared by personnel not involved in the study.

The BP (systolic, diastolic and mean) and heart rate before start of skin closure were recorded as the baseline values. At the start of skin closure volatile anaesthetic was cut off. Residual neuromuscular blockade was reversed at the end of surgery with neostigmine methyl sulphate (0.05 mg/kg body weight) and atropine sulfate (0.02mg/kg body weight) administered intravenously. Once the patient started breathing regularly nitrous oxide was discontinued. The study drug was then administered a minimum of 3 minutes after reversing the patient over a period of 60 seconds. The trachea was extubated a minimum of two minutes after administration of study drug. All patients were administered 100% oxygen by face mask and heart rate, blood pressure were recorded every minute for a period of five minutes. The patients were monitored in recovery room for a period of at least 30 minutes.

Ease of tracheal extubation:

The quality of tracheal extubation was evaluated using a three point rating scale.

1 = no cough or straining.
2 = minimal coughing.
3 = high degree of coughing or straining.

All values were expressed as mean± SD. Differences in hemodynamic variables were determined by ANOVA. If ANOVA detected differences post hoc

analysis was performed with t-tests to examine intragroup differences. All post hoc comparisons were adjusted appropriately using Bonferroni's correction. A p value of < 0.05 was considered significant.

OBSERVATION AND RESULTS

Sixty patients under this study were categorized into three groups. 20 in each group. They comprised both sexes in the age group 16 to 60 years. The demographic profile is as follows:

Characteristics	**Group – D (Diltiazem)**	**Group – L (Lignocaine)**	**Group D – L (Diltiazem and Lignocaine).**
Age (Years)	35.83 ± 12.26	35.37 ± 11.49	33.63 ± 11.50
Sex	M – 11 F – 9	M – 13 F – 7	M – 11 F – 9
Weight (Kgs.)	54.67 ± 7.90	55.68 ± 8.24	55.32 ± 7.89
Duration of anaesthesia (min)	110.56 ± 22.55	110.00 ± 31.22	116.32 ± 20.87
Basal heart rate (bpm)	80.44 ± 8.66	76.74 ± 7.12	77.47 ± 7.29
Basal systolic blood pressure (mm Hg)	123.67 ± 6.90	121.05 ± 8.70	121.58 ± 6.91
Basal diastolic blood pressure (mm Hg)	83.17 ± 6.49	81.79 ± 7.60	80.21 ± 6.03
Total dose of fentanyl (µg)	133.06 ± 21.15	136.05 ±26.85	144.21 ± 21.55
Total dose of Vecuronium (mg)	9.67 ± 1.53	10.11 ± 1.97	10.37 ± 1.42
Blood loss (ml)	135.55 ± 8.07	140.73 ± 12.59	137.89 ± 10.44

Age Group (Years)

GROUP	N	Mean	Standard Deviation	F-test
D	20	35.83	12.26	F = 0.18 P = 0.83
L	20	35.37	11.49	
D – L	20	33.63	11.50	

In the Group D, the mean age was 35.83 $\pm$ 12.26 years, ranging from 18 years to 58 years. In the Group L the mean age was 35.37 $\pm$ 11.49 years, the range being 18 years to 55 years and in the Group D – L, it was 33.63 $\pm$ 11.50 years, the range being 18 years to 53 years. Thus there was no significant difference between the three groups as their p = 0.83 (p value of significance being < 0.05).

Sex Distribution

Sex	Group – D	Group – L	Group D – L	Total
Male	11	13	11	35
Female	9	7	9	25
Total	**20**	**20**	**20**	**60**

$\chi^2 = 0.55$ p = 0.77 (p value of significance being < 0.05).

The sex distribution between the three groups is equal as shown in the bar chart,

the difference being insignificant (p = 0.77).

Weight Distribution (Kgs)

GROUP	N	Mean (kgs)	Standard Deviation	*F-test*
D	20	54.67	7.90	F = 0.07 P = 0.93
L	20	55.68	8.24	
D – L	20	55.32	7.89	

In the group D, the mean weight was 54.67 ± 7.90 Kg ranging from 40 Kg to 65 Kg. In the Group L, the mean weight was 55.68 ± 8.24 Kg, the range being 42 Kg to 76 Kg and in group D – L the mean weight was 55.32 ± 7.89 Kg, the range being 40 Kg to 72 Kg. Thus there was no significant difference between the three groups as their p value = 0.93.

Baseline Hemodynamic Parameters

There was no statistically significant difference in the baseline hemodynamic parameters between the three groups.

Basal Heart Rate (bpm)

GROUP	N	Mean	Standard Deviation	F-test

D	20	80.44	8.66	F = 3.03 P = 0.08
L	20	76.74	7.12	
D – L	20	77.47	7.29	

Basal Systolic Blood Pressure (mm Hg)

GROUP	N	Mean	Standard Deviation	F-test
D	20	123.67	6.90	F = 0.61 P = 0.55
L	20	121.05	8.70	
D – L	20	121.58	6.91	

Basal Diastolic Blood Pressure (mm Hg)

GROUP	N	Mean	Standard Deviation	F-test
D	20	83.17	6.49	F = 0.89 P = 0.42
L	20	81.79	7.60	
D – L	20	80.21	6.03	

There was also no statistically significant difference for the total dose of opioid (fentanyl citrate) or muscle relaxant (Vecuronium) used between the groups.

Total dose of fentanyl (µg).

GROUP	N	Mean	Standard Deviation	F-test

D	20	133.06	21.15	F = 1.13 P = 0.33
L	20	136.05	26.85	
D – L	20	144.21	21.55	

Total dose of Vecuronium (mg)

GROUP	N	Mean	Standard Deviation	F-test
D	20	9.67	1.53	F = 0.84 P = 0.44
L	20	10.11	1.97	
D – L	20	10.37	1.42	

Heart Rate (bpm)

GROUP	Base line	IMIN after Study Drug Admn	Tracheal Extubation					
			Immediate	1 min.	2 min	3 min	5 min	REC room
D	83.00 ± 9.43	98.83 ± 11.55	100.78 ± 15.10	91.67 ± 14.52	85.67 ± 13.53	81.72 ± 11.69	81.17 ± 10.67	81.56 ± 10.85
L	83.21 ± 9.13	92.16 ± 10.04	99.95 ± 10.23	90.63 ± 12.70	84.42 ± 11.07	80.37 ± 10.17	78.32 ± 8.30	76.89 ± 7.19
D – L	87.05 ± 10.97	89.26 ± 9.66	87.95 ± 9.02	81.37 ± 7.62	79.37 ± 8.93	78.32 ± 8.16	77.42 ± 7.27	77.16 ± 6.78

The arithmetic mean of the baseline heart rate for the D , L and D-L groups were 83.00 ± 9.43, 83.21 ± 9.13 and 87.05 ± 10.97 beats per min respectively. There was no statistically significant difference between the mean baseline heart rates for the

three groups (p = 0.37).

The heart rate increased in all the three groups after extubation and this increase was maximal immediately after extubation.

In the D group the increase in heart rate above the baseline was statistically significant 1 min after administration of study drug (p = 0.002) and immediately after tracheal extubation (p = 0.000). Even though the heart rate in the 1st min & 2nd min after tracheal extubation was higher than baseline, this increase was statistically not significant (p = 0.51[1st min], p = 1.00 [2nd min]). The heart rate dipped below the baseline value by the third minute and this decrease was statistically not significant in the third (p = 1.000) and fifth minute (p=1.000).

In the L group the increase in the heart rate over the baseline was statistically significant immediately after tracheal extubation (p = 0.000). The heart rate remained over the baseline till 2 min after tracheal extubation. The heart rate dipped below the baseline from the third min after tracheal extubation. This decrease was not statistically significant.

In the D-L group the heart rate increased above the baseline immediately after tracheal extubation. This increase was not statistically significant (p = 1.000). The heart rate dipped below the baseline by the first minute but this decrease was not statistically significant. The decrease in the heart rate in the second, third & fifth minute after tracheal extubation was also not statistically significant (p=1.000).

The mean heart rates of the D,L & D-L groups in the recovery room were 81.56 ± 10.85, 76.89 ± 7.19 and 77.16 ± 6.78 beats per minute respectively which were not statistically significant (p = 0.180).

Systolic Blood Pressure (mm Hg)

GROUP	Base line	IMIN after Study Drug Admn.	Tracheal Extubation					
			Immediate	1 min.	2 min	3 min	5 min	REC room
D	123.06 ± 11.09	131.61 ± 10.66	132.28 ± 10.91	122.67 ± 11.85	118.22 ± 10.00	118.61 ± 8.35	118.94 ± 8.38	118.72 ± 7.95
L	120.00 ± 9.84	128.68 ± 8.71	134.74 ± 8.90	126.53 ± 11.99	120.21 ± 11.03	119.21 ± 9.44	119.05 ± 9.63	119.32 ± 8.62
D – L	120.00 ± 6.64	123.58 ± 8.25	124.89 ± 7.41	117.95 ± 9.11	116.42 ± 6.56	117.79 ± 6.79	118.32 ± 6.93	118.11 ± 6.26

The mean baseline systolic blood pressure for the D, L and D-L groups were 123.06 ± 11.09, 120.00 ± 9.84 and 120.00 ± 6.64 mm Hg respectively. There was no statistically significant difference (p = 0.52) between the mean baseline systolic blood pressure of the three groups.

It is apparent from the table that systolic blood pressure increased in all the three groups after extubation and this increase was maximal immediately after tracheal extubation.

The increase in systolic blood pressure from the baseline value was not significant in the D group in the first 5 min after extubation. The systolic blood

pressure decreased to less than the baseline value in the D group by the second minute, but this decrease was not statistically significant (P= 1.000).

In the L group, the increase in the systolic blood pressure over the baseline value was significant immediately after tracheal extubation (p=0.000). The systolic blood pressure touched the baseline in the second minute after extubation. The SBP decrease below the baseline by the third minute after extubation, but this was not statistically significant (P = 1.000).

In the D – L group, the systolic blood pressure increased above the baseline immediately after tracheal extubation which was not statistically significant (p = 1.000). The systolic blood pressure dipped below the baseline value from the first minute after tracheal extubation which was also not statistically significant (p = 1.000).

The mean systolic blood pressures in the recovery room were 118.72 $\pm$ 7.95, 119.32 $\pm$ 8.62 and 118.11. $\pm$ 6.26 mm Hg for the D, L & D - L groups respectively which were statistically not significant (P=0.889).

Diastolic Blood Pressure (mm Hg)

GROUP	Baseline	IMIN after Study drug Admn.	Tracheal Extubation					
			Immediate	1 min.	2 min	3 min	5 min	REC room
D	84.94 ± 10.38	87.50 ± 10.39	86.56 ± 11.58	79.67 ± 10.49	80.94 ± 10.45	82.72 ± 11.89	81.78 ± 12.01	82.06 ± 11.47
L	79.21 ± 9.11	86.89 ± 8.39	90.26 ± 8.39	82.84 ± 9.72	81.84 ± 9.72	78.95 ± 10.65	77.11 ± 9.51	77.11 ± 10.00
D – L	82.11 ± 9.07	83.89 ± 7.10	83.79 ± 6.99	78.00 ± 10.89	76.26 ± 8.04	79.05 ± 5.64	77.00 ± 6.64	76.68 ± 4.92

The arithmetic mean of the baseline diastolic blood pressures for the D, L & D-L groups were 84.94 ± 10.38, 79.21 ± 9.11, 82.11 ± 9.07 mm Hg. respectively. There was no statistically significant difference between the three groups (p = 0.19).

In the D group, the diastolic blood pressure increased immediately after tracheal extubation which was not statistically significant (p=1.000). The diastolic blood pressure decreased below the baseline value from the first minute after tracheal extubation.

In the L group, there was an increase in the diastolic blood pressure from the baseline value immediately and in the first two minutes after tracheal extubation. This increase was statistically significant (p = 0.012) immediately after tracheal extubation. The diastolic blood pressure decreased below the baseline value by the third minute after extubation and continued to do so for the remaining period of study.

In the D-L group the diastolic blood pressure decreased below the baseline value from the first minute after extubation and continued to be below the baseline for the remainder of the study. This decrease was statistically not significant.

The arithmetic mean of the diastolic blood pressures of the D, L & D – L groups in the recovery room were 82.06 ± 11.47, 77.11 ± 10.00 and 76.68 ± 4.92 mm Hg respectively. There was no significant difference between the diastolic blood pressures in the three groups in the recovery room ($p = 0.154$).

SMOOTHNESS OF EXTUBATION

7 patients out of twenty in the D group (35%) and 1 patient out of twenty (5%) in the L group & D – L group had a grade 3 extubation response – significant coughing and straining.

11 patients in the D group (55%), 14 patients in the L group (70%) and 13 patients in the D– L group (65%) had grade 2 extubation response - minimal coughing .

2 patients in the D group (10%), 5 patients in the L group (25%) and 6 patients in the D-L group (30%) had grade 1 extubation response – no coughing (smooth extubation).

DISCUSSION

Hypertension and tachycardia usually accompany laryngoscopy and tracheal intubation. Similar hemodynamic changes can occur during emergence from anaesthesia and tracheal extubation. Even though these responses are brief and well tolerated by the majority of patients they can be detrimental and cause significant clinical problems in susceptible patients. This is especially so in patients with ischemic heart disease, neurosurgical patients and hypertensive patients who demonstrate an exaggerated response to tracheal extubation which could prove detrimental in the outcome.

Studies have shown the importance of maintaining stable hemodynamic parameters intraoperatively in high-risk patients. In the study by Slogoff and Keats in patients undergoing coronary artery bypass surgery, they were able to demonstrate that the incidence of perioperative myocardial ischemia was related to the number of

episodes of intraoperative tachycardia[34]. Asiddao et al studied the factors associated with perioperative complications - neurological deficits, myocardial infraction and mortality in patients undergoing carotid endarterectomy[35]. They found out that the perioperative factors that unfavorably affected the neurological outcome following carotid endarterectomy included poor perioperative blood pressure control. They concluded that strict regulation of blood pressure not only during the surgical period but also before and after surgery is extremely important in these high-risk patients.

Various pharmacological methods have been used to attenuate the circulatory responses to tracheal extubation. These include use of intravenous lignocaine[6], fentanyl[9], alfentanil, esmolol[8] and labetolol.

Many studies have reported a beneficial effect of calcium channel blockers in attenuating the cardiovascular changes during tracheal extubation and emergence from anaesthesia. Milkawa and Nishina[35] demonstrated that both verapamil and diltiazem attenuated the increases in heart rate and arterial blood pressure during and after tracheal extubation and the inhibitory effect was greatest with verapamil 0.1mg/kg.

Fuji and Kihara[36] compared the inhibitory effects of calcium channel blockers, nicardipine and diltiazem on hemodynamic changes after tracheal extubation in hypertensive patients. They concluded that administration of diltiazem produced greater attenuation of the circulatory responses to tracheal extubation than nicardipine.

Nishina and Mikawa[37] in their study compared the effects of intravenous

diltiazem and lignocaine on hemodynamic changes during tracheal extubation. They concluded that a bolus dose of intravenous diltiazem 0.1 or 0.2 mg/Kg given 2 minutes before extubation attenuated the cardiovascular changes occurring in association with tracheal extubation. This effect of diltiazem was equal or superior to that of intravenous lignocaine.

As reported by Nishina and Mikawa a combination of lignocaine and diltiazem would attenuate hemodynamic changes to more tolerable levels than each drug administered alone because the mechanisms whereby these two drugs attenuate tachycardia and hypertension are thought to be different. Hence this study was designed to compare the efficacy of combination of diltiazem and lignocaine with each drug alone in attenuating the hemodynamic changes during tracheal extubation.

The rationale for the use of diltiazem at dose of 0.1mg/kg was based on the following findings -

(i) Diltiazem 0.1 – 0.2 mg/Kg has been used to treat supraventricular tachycardic arrhytmia [38,39] or unstable angina[40]

(ii) Intravenous diltiazem at doses of 0.09 – 0.23 mg/kg has been used to reduce abrupt circulatory changes in response to various surgical stimuli.

(iii) Indian patients require a lower dose of intravenous diltiazem as compared to western counterparts (0.1 mg/kg versus 0.25-0.33 mg/kg) which gives a prompt & effective response in patients with supraventricular tachyarrhythmias[42] Mikawa et al reported one episode of profound hypotension (SBP = 71 mmHg) when diltiazem was used in a dose of 0.3 mg/kg for attenuating hemodynamic responses to tracheal

extubation.

The onset and duration of action of diltiazem are rapid and short. The MAP begins to decrease 20-40 sec after administration of intravenous diltiazem with a peak effect occurring at 1.5-2min[43]. Lignocaine in a dose of 1-2 mg/kg body weight has been used to blunt the pressor response to intubation. It has been recommended to be given 90 sec prior to intubation. Fujii et al confirmed that MAP begins to increase immediately after tracheal extubation and reaches a maximum value within one minute when no medication is provided[23]. Thus the timing of administration of the study drug (two minutes before tracheal extubation) was chosen in this study.

Intravenous administration of the mixture of neostigmine and atropine increases heart rate within 1 minute, the effect peaking 1-2min after injection. The heart rate returns to basal values 3 minutes after injection and decreases further until 6 min after dosing (44). In my study the intravenous administration of study drug was after 3 minutes of injection of neostigmine-atropine mixture and the extubation response was analyzed up to five minutes. Hence the early increase in heart rate induced by atropine was likely to be excluded.

HEART RATE CHANGES:

In Group D, the increase in mean heart rate recorded immediately after tracheal extubation was statistically significant from the baseline value showing that the attenuation of stress response by diltiazem to extubation was not adequate. This

finding was in concurrence with the study done by Fujii et al.

In Group L, there was a statistically significant increase in the mean heart rate from the baseline to that recorded immediately after tracheal extubation. This showed that there was inadequate attenuation of stress response by lignocaine in Group L. This finding was in concurrence with the study done by Fujii et al.

Patients in Group D-L who received both diltiazem and lignocaine,eventhough showed a slight increase in heart rate from the baseline it was not statistically significant. The increased heart rate recorded is also the least among the groups. This finding was also in concurrence with the study made by Fujii et al.

Since the increase in mean heart rate was the least in Group D-L, it can be concluded that the attenuation of the stress response to tracheal extubation is best achieved by a combination of diltazem 0.1mg/kg and lignocaine 1.5mg/kg given 2 minutes before extubation.

SYSTOLIC BLOOD PRESSURE (SBP) CHANGES:

In-group D where diltiazem was given 2 minutes before tracheal extubation the increase in mean SBP immediately after tracheal extubation (132.28 $\pm$ 10.91mmHg) was not statistically significant from baseline value. This showed that the pressor response to tracheal extubation was adequately attenuated in this group.

In group L where lignocaine was given, the cardiovascular response to tracheal

extubation was not attenuated as shown by the statistically significant increase in the mean SBP values (134.74 ± 8.90mmHg) recorded immediately after tracheal extubation from the baseline value. This finding was in concurrence with the study done by Fujii et al.

In Group D-L, the increase in mean SBP immediately after tracheal extubation was the least among the four groups (124.89 ± 7.41 mmHg). This increase was not statistically significant proving that the pressor response to tracheal extubation was adequately obtunded by combination of diltiazem and lignocaine.

From the above finding both Group D and Group D-L showed adequate attenuation of pressor response to tracheal extubation. Since the increase in mean SBP immediately after tracheal extubation was the least in Group D-L, it can be concluded that the pressor response to tracheal extubation is best attenuated when both diltiazem (0.1mg/Kg) and lignocaine (1.5mg/kg) are given in combination 2 minutes before tracheal extubation.

DIASTOLIC BLOOD PRESSURE (DBP) CHANGES:

In Group D, the increase in mean DBP following tracheal extubation was not statistically significant from the baseline value. Patients in Group L showed significant increase in DBP following tracheal extubation. Patients in Group D-L showed the maximum attenuation of DBP changes which follow tracheal extubation.

SMOOTHNESS OF EXTUBATION

The diltiazem group had significantly greater episodes of severe coughing or straining (grade 3). The diltiazem group also had fewer smooth extubation (grade 1) as compared to the other two groups. Intravenous lignocaine is known to suppress the cough reflex in both awake and anaesthetized patients. The exact mechanism of action of the antitussive effect of intravenous lignocaine is not known but could be either due to local anaesthetic effect in the pharynx or due to an action in the central nervous system.

Steinhaus et al studied the effectiveness of intravenous lignocaine in suppressing the cough reflex of anaesthetized patients who were intubated but spontaneously breathing[45]. Lignocaine prevented cough in eight of the ten patients stimulated by manual displacement of the endotracheal tube. Poulton et al studied the ability of intravenous lignocaine in awake individuals in whom coughing was induced by citiric acid aerosol inhalation to suppress the cough reflex[46.] They found out that intravenous lignocaine had a significant effect in decreasing the cough responses of awake unmedicated subjects. Yukioka et al studied the dose and plasma levels of lignocaine required to suppress coughing during tracheal intubation. They concluded that coughing was eliminated with plasma concentrations of lignocaine in excess of 3μg/ml. Because of its antitussive effect lignocaine was commonly used during recovery from anaesthesia for neurosurgical and certain ophthalmologic procedures.

Episodes of perioperative hypertension and tachycardia with its consequent ill

effects on the vital organs can be a significant problem in some patients despite adequate depth of anaesthesia and analgesia. Bolus intravenous doses of β-blockers are usually used in such situations. In case of co-existing reactive airway disease one would hesitate to administer β-blockers. This study shows that bolus doses of diltiazem and lignocaine can be safely administered in such situations leading onto normalization of hypertension and tachycardia.

SUMMARY

This prospective randomized study was designed to evaluate the efficacy of combination of diltiazem and lignocaine in suppressing the hemodynamic changes during tracheal extubation. The effect of Diltiazem-Lignocaine combination was compared with that of Diltiazem and Lignocaine given individually.

A total of sixty patients belonging to ASA physical status 1 and 2 were randomly divided into three groups. Patients in Group D received Inj.Diltiazem 0.1mg/ kg, patients in Group L received Inj.Lignocaine 1.5mg/kg and patients in Group D-L received both Inj.Diltiazem 0.1mg/kg and Inj.Lignocaine 1.5mg/kg. Tracheal extubation was done two minutes after administration of study drug. Changes in heart rate and blood pressure were measured up to five minutes after tracheal extubation.

The following observations were made

- Patients in Group D-L showed the maximum attenuation of heart rate and blood pressure changes following tracheal extubation..
- Patients in Group D showed a significant increase in heart rate ($p < 0.05$) after extubation but the increase in blood pressure was not significant.
- Patients in Group L showed significant increase in both heart rate and blood pressure following tracheal extubation.
- The percentage of patients who had significant coughing and straining during extubation was greater in Group D than in the other two groups.
- No patients in any of the three groups developed laryngeal spasm, profound hypotension(SBP < 80mmHg) or bradycardia (HR < 50 bpm).

CONCLUSION

From the above study it is concluded that the hemodynamic changes associated with extubation of trachea can be effectively obtunded by using a combination of Diltiazem and Lignocaine than giving each drug separately.

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ATTENUATION OF HEMODYNAMIC RESPONSES TO TRACHEAL EXTUBATION : COMPARISON OF DILTIAZEM, LIGNOCAINE AND DILTIAZEM-LIGNOCAINE COMBINATION.

NAME: AGE/SEX :

IP NO : UNIT :

DIAGNOSIS: ANAESTHESIOLOGIST:

NAME OF THE OPERATION :

HISTORY IN BRIEF :

Previous anaesthetic experience :
Drug allergy :
Others :

GENERAL EXAMINATION :

Weight :

Oedema / pallor / icterus / clubbing / lymphadenopathy

PR :

BP :

SYSTEMIC EXAMINATION :

CVS :

RS :

CNS :

AIRWAY :

INVESTIGATIONS :

Hb :

RBS/FBS :

Blood urea :

Serum creatinine :

Chest X-Ray :

ECG :

INCLUSION CRITERIA :

-ASA 1 & ASA 2 patients between ages of 16 and 60 years.

EXCLUSION CRITERIA :

-Patients with coexisting cardiovascular diseases or on cardiovascular drugs

-Patients with heart rate less than 60 beats/min

-Patients with blood pressure less than 100/60 mmHg

-Patients with documented hepatic or renal disease.

PREMEDICATION :

Tab Diazepam 10 mg PO ; HS night before surgery.

Tab Ranitidine 150 mg PO ; 6AM on day of surgery.

Inj.Atropine– 20µg/kg im 45 min before surgery

PREOXYGENATION :

With 100% oxygen for 3 min.

INDUCTION OF ANAESTHESIA :

Anaesthesia induced with Inj.Thiopentone 5mg/kg and Inj.Fentanyl citrate 2µg/kg . Tracheal intubation was facilitated by intravenous administration of Vecuronium 0.1mg/kg. Anaesthesia maintained with Isoflurane(0.5-1%) and Nitrous oxide(66%) in O2. Supplemental doses of Fentanyl and Vecuronium were administered as required.

Patients were randomly allocated to one of the three groups before the end of surgery.

GROUP D : 0.1mg/kg body weight of Diltiazem plus Saline.

GROUP L : 1.5 mg/kg body weight of Lignocaine plus Saline.

GROUP D-L : 0.1 mg/kg Diltiazem plus 1.5 mg/kg of Lignocaine.

These medications were given a minimum of 3min after reversing the patient with Inj.Neostigmine (0.05 mg/kg) & Inj.Atropine(0.02mg/kg). Trachea was extubated a minimum of 2 min after administration of study drug.

Total dose of Fentanyl(µg) :

Total dose of Vecuronium(mg) :

Blood loss :

	SYSTOLIC BP (mmHg)	DIASTOLIC BP (mmHg)	HEART RATE (bpm)

Baseline value			
Administration of study drug			
1min after admn of study drug			
Tracheal extubation			
Post extubation(1min)			
Post extubation(2min)			
Post extubation(3min)			
Post extubation(5min)			

Smoothness of extubation :

Grade 1 : No coughing

Grade 2 : Minimal coughing

Grade 3 : Significant coughing/straining.

Recovery room HR : BP :

Complications if any :