"A COMPARATIVE STUDY OF CLONIDINE AND GABAPENTIN FOR ATTENUATING HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION"

By

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Under the guidance of

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
bpm	beats per minute.
CNS	Central Nervous System
CVS	Cardiovascular System
DBP	Diastolic Blood Pressure
ECG	Electro Cardio Gram
GABA	gamma amino butyric acid
HR	Heart Rate
Hrs	Hours
Inj.	Injection
i.v.	intravenous
IOP	intraocular pressure
Kg	Kilogram
L	litres
LMA	laryngeal mask airway
MAP	mean arterial pressure
mg	Milligram
Min	Minutes

mm of Hg	millimetre of mercury
NIBP	Non Invasive Blood Pressure
RPP	Rate pressure product
SBP	Systolic Blood Pressure
SD	Standard Deviation
SpO_2	Percentage of Oxygen Saturation
µg	microgram
yrs	years

ABSTRACT

Introduction

Laryngoscopy and intubation are associated with stress response changes like tachycardia, hypertension and dysrythmias .Studies have reported 10%– 18% of the patients develop ischemic ST segment changes during laryngoscopy which are well tolerated and reversible in healthy adults.Many studies have shown Clonidine, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation. Gabapentin, is a newer drug being used as an antiepileptic . Recently few studies have shown it to be useful for attenuation of intubation responses.

Objectives

1. To assess the efficacy and compare oral clonidine and gabapentin premedication for attenuation of hemodynamic responses following laryngoscopy and tracheal intubation.
2. To assess side effects associated with the drugs.

Methodology

Sixty patients in the age group of 18 to 50 years were selected for study. Patients were randomly divided **.**

Patients received Gabapentin or Clonidine 120 minutes before surgery.

Group "C" - 200µg clonidine .

Group "G" - 900mg gabapentin .

Baseline parameters like pulse rate and systolic blood pressure, diastolic blood pressure, mean blood pressure , oxygen saturation and ECG were recorded.

The level of sedation was assessed by a four point score.

After pre-oxygenation, pre medication was done with 5 µg/kg of i.v glycopyrolate. 2.5 µg/kg i.v Fentanyl was given for analgesia. Patient was induced with i.v Thiopentone 5 mg/kg followed by i.v suxamethonium 2 mg/kg for intubation. Anaesthesia was maintained with N_2O+O_2+Isoflurane(0.6-1%). Muscle relaxation was achieved with i.v Vecuronium. The heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were recorded at 0,1,3,5 and 10 minutes after endotracheal intubation. Statistical Analysis was done by Students t test, Chi square test and Fisher exact test

Results

Demographic data in both group were not statistically significant. At 1 and 3 minutes there was no difference between both the groups regarding heart rate changes but at 5 and 10 minutes heart rate response to laryngoscopy and intubation in the clonidine group was clinically lesser than gabapentin group and statistically highly significant. SBP, DBP and MAP was significantly lower in gabapentin group compared with clonidine at 1, 3, 5 and 10 mins ($p<0.001$).

The mean sedation scores was found to be clinically and statistically more in Clonidine group than Gabapentin group. Side effects like drowsiness and bradycardia were more with clonidine.

Conclusion

Gabapentin is a better drug compared to clonidine to attenuate the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated.

Keywords: Gabapentin, Clonidine, Intubation, Hemodynamic Response

TABLE OF CONTENTS

LIST OF FIGURES AND GRAPHS

LIST OF TABLES

INTRODUCTION

Since the inception of general anaesthesia it has been well recognised that laryngoscopy followed by tracheal intubation is a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory and other physiological systems. Significant tachycardia, hypertension and dysrhythmias can occur with tracheal intubation.[1]Out of the various techniques employed, general anaesthesia is the one which is routinely and frequently practiced employing various inhalational and intravenous agents to achieve a state of unconsciousness.

With the loss of consciousness caused by general anaesthesia, there is a loss of protective airway reflexes such as coughing, loss of airway patency and sometimes loss of a regular breathing pattern due to the effect of anaesthetics. To maintain an open airway and regulate breathing within acceptable parameters, an endotracheal tube is inserted into the trachea after the patient is unconscious.

The magnitude of cardiovascular response is directly related to the force and duration of laryngoscopy.[2]Many studies have reported that 10%– 18% of the patients develop ischemic ST segment changes during the procedure.[3]Though these undesirable changes are transitory in nature and well tolerated in healthy individuals,it may result in potentially deleterious effects in patients with co-morbid conditions like hypertension, raised intracranial pressure or coronary artery disease.

As laryngoscopy followed by endotracheal intubation has become the sine qua non of safe anaesthesia, it has become absolutely necessary to take steps to minimize the adverse cardiovascular effects associated with it.

The hemodynamic responses during laryngoscopy and endotracheal intubation should be abolished to balance the myocardial oxygen supply and demand which is a key note in the safe conduct of anaesthesia.

Many studies have shown Clonidine, a selective α2 adrenoceptor agonist with sedative and analgesic effects, to be an effective drug for attenuation of hemodynamic responses to laryngoscopy and intubation.[4]

Gabapentin is a newer drug being used as an antiepileptic.In addition, it has been shown to be effective in neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy.[5]Furthermore, a growing body of evidence suggests that perioperative administration is efficacious for postoperative analgesia, preoperative anxiolysis and preventing chronic post-surgical pain, postoperative nausea and vomiting and delirium.Recently, few studies have shown it to be useful for attenuation of intubation responses.

At present there are very few studies comparing oral Clonidine and Gabapentin premedication for attenuation of hemodynamic responses following laryngoscopy and intubation.So this study is undertaken to evaluate the efficacy of Gabapentin in attenuating hemodynamic responses to laryngoscopy and intubation and how it fares in comparison with Clonidine.

OBJECTIVES OF THE STUDY

1. To assess the efficacy and compare oral Clonidine and oral Gabapentin premedication for the attenuation of hemodynamic responses following laryngoscopy and tracheal intubation.
2. To assess side effects like sedation associated with the drugs.

REVIEW OF LITERATURE

REVIEW OF CLINICAL STUDIES

A randomised control study was done by Marashi SM and colleagues in 2009 to evaluate the effect of oral clonidine 200 micrograms and gabapentin 900mg premedication in modifying the hyperdynamic response following laryngoscopy and tracheal intubation on seventy-five ASA I-II patients where Group-1 received 0.2 mg clonidine, Group-2 received placebo and Group-3 received 900 mg gabapentin, 120 minute before operation. Heart rate, systolic, diastolic and mean arterial blood pressure were measured before induction of anesthesia, before laryngoscopy, and 1, 3, 5, 10 min after intubation. The highest rates of heart rate, systolic, diastolic and mean arterial blood pressure were in the placebo group and in one minute after laryngoscopy, and the lowest rate were in the gabapentin group at the time of 1, 3, 5 and 10 after laryngoscopy, except that the lowest rate of heart rate in 10 min after laryngoscopy was in clonidine group.Their data proposed that both clonidine and gabapentin have effective role in blunting hyperdynamic responses after laryngoscopy, more so with gabapentin.[6]

Previously Shrestha GS, Marhatta MN, Amatya R did a prospective research on the Use of Gabapentin, Esmolol or Their Combination toAttenuate Haemodynamic Response to Laryngoscopy and Intubation on 72 patients and found thatWhen compared with baseline values, in Group Gabapentin, there was significant increase in heart rate, but the systolic blood pressure was decreased at 5 and 10 minutes and mean arterial pressure was decreased at 5 minutes. They showed that although gabapentin

does decrease the SBP, DBP and MAP, the combination of gabapentin 1200mg and esmolol 1.5mg/kg is safer and better attenuates both the heart rate and blood pressure response to laryngoscopy and intubation.[7]

Bafna U, Goyal VK, Garg A in a prospective double blind randomised study compared two different doses of gabapentin 600mg and 1000mg to attenuate hemodynamic responses to laryngoscopy and tracheal intubation in 90 patients and found that gabapentin 1000mg given 1 hour prior to surgery attenuated hemodynamic response to laryngoscopy and tracheal intubation better than 600mg ($p<0.001$).[8]

In yet another prospective double blind randomised study done by Iftikhar T and colleagues oral gabapentin 800mg decreased the hemodynamic response to direct laryngoscopy and tracheal intubation on systolic blood pressure at 2mins and 15 mins , mean arterial pressure at 2mins, 10mins ,and 15 mins and heart rate at 10 mins and 15 mins following laryngoscopy.[9]

In a prospective randomised study done by Montazeri K oral Clonidine versus Oral Gabapentin premedication, showed that HR and RPP significantly decreased in Gabapentin group and Group Clonidine at 5, 10, and 15 minutes after tracheal intubation compared with those just before laryngoscopy ($p < 0.05$) but compared with Clonidine, Gabapentin significantly reduced DAP, SAP, MAP, and RPP changes for 15 min after endotracheal intubation. Compared with placebo, the incidence of HR, SAP, DAP, and MAP percent increase ($\geq$ 20% of baseline values) were significantly lower in Group Gabapentin but not so with Clonidine group when compared to placebo group. [10]

Another study done by Fassoulaki and colleagues in 2006, demonstrated that gabapentin 1600 mg given in four divided doses, at 6 h intervals (starting the day before surgery) attenuated the pressor response but not the tachycardia, associated with laryngoscopy and tracheal intubation.[11]

Ali AR studied the efficacy of preoperative oral gabapentin in a dose of 1200mg for attenuation of neuroendocrine response to laryngoscopy and endotracheal intubation. They found that gabapentin suppressed the hemodynamic responses (HR and BP) at 1,2,3,4,5 and 10 mins after intubation but these effects weren't caused by inhibition of catecholamine response.[12]

Memis and co workers in 2006 studied the effect of Gabapentin on mean arterial pressure and heart rate at induction of anaesthesia and tracheal intubation on Ninety normotensive patients (ASA I) undergoing elective surgery divided into three groups of 30 patients each. Patients received oral placebo (Group I), 400 mg of gabapentin (Group II) or 800 mg of gabapentin (Group III) 1 hour prior to surgery in the operating theatre. After induction of anaesthesia heart rate and mean arterial pressure were recorded at baseline 1, 3, 5, 10 and 15 min after intubation. Patients receiving placebo and 400 mg gabapentin showed a significant increase in blood pressure and heart rate associated with tracheal intubation compared to baseline levels and from patients receiving 800 mg of gabapentin. There was a significant decrease in heart rate and mean arterial pressure in the group receiving 800 mg gabapentin 1, 3, 5 and 10 min after intubation compared to the placebo group and 400 mg gabapentin group. ($p<$

0.001, $p < 0.001$, $p < 0.05$ and $p < 0.05$, respectively compared to Groups gabapentin 400mg and placebo.[13]

Gupta K, Sharma D and GuptaPK did a comparative double blind randomised study about the clinical efficacy of Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy. In this study Oral premedication with pregabalin 150 mg or clonidine 200 μg caused sedation and anxiolysis with hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy, without prolongation of recovery time and side effects. They showed that clonidine group showed slight but statistically significant decrease in heart rate before induction. The heart rate increased significantly immediately after laryngoscopy in control group (135.6±7.26), whereas no such changes were observed in pregabalin group and in clonidine group. There was statistically significant attenuation of heart rate in premedicated groups ($P<0.0001$), after laryngoscopy. Decreased amount of propofol and fentanyl was required for induction in premedicated groups as compared with control group. Three patients of clonidine group developed bradycardia (HR <56 beats min^{-1}) 15 minutes after intubation and were treated with adequate dose of i.v. atropine. [14]

Kaya and colleagues who studied the effect of preoperative gabapentin 800 mg, given 2 hr before surgery on intraocular pressure (IOP) and haemodynamic changes in response to endotracheal intubation and concluded that pretreatment with gabapentin 800 mg effectively suppressed the increase in intraocular pressure and attenuated the increase in the MAP but not the HR associated with tracheal intubation.[15]

Kiran S, Verma D in their study in compared tab. Gabapentin 800mg and placebo as regards to attenuation of hemodynamic responses following direct laryngoscopy and tracheal intubation. They showed that SBP, DBP and MAP were significantly low as compared with placebo in patients pretreated with gabapentin but the tachycardiac response was not completely eliminated. None of their patients exhibited hypotension before induction of anaesthesia.[16]

Kong VK in 2007 published an article about the gabapentin: a multimodal perioperative drug? and suggested that perioperative administration of gabapentin is efficacious for postoperative analgesia, preoperative anxiolysis, attenuation of the haemodynamic response to laryngoscopy and intubation, and preventing chronic post-surgical pain, postoperative nausea and vomiting and delirium. This article reviews the clinical trial data describing the efficacy and safety of gabapentin in the setting of perioperative anaesthetic management. They concluded that Gabapentin, as a potential multimodal perioperative drug, could be given in the dose of 900 mg 1–2 h before surgery. [17]

Koc and co workers studied the effect of gabapentin, dexamethasone and their combination in patients undergoing varicocele surgery. They found that heart rate and mean arterial pressure values were significantly lower in the group receiving both gabapentin and dexamethasone at 1, 3, 5 and 10 min after intubation than in the group receiving dexamethasone or gabapentin alone. The MAP and HR in gabapentin group were lower than the placebo group. [18]

Sharma and colleagues in a a prospective randomised study titled Comparative Evaluation Of Gabapentin, Clonidine And Combination Of Both The Drugs To Attenuate The Pressor Response To Direct Laryngoscopy And Intubation showed that Given 60 minutes before induction of General Anaesthesia, oral Gabapentin and Clonidine in the dose of 800mg and 300µg respectively, attenuate the pressor response but gabapentin blunts the increase in arterial blood pressure better than clonidine. The combination of these two drugs in the studied dosage was not effective in attenuating the pressor response to laryngoscopy and intubation. [19]

Dipak L. Raval and colleagues in their study to compare effectiveness of oral clonidine(4 µg/kg) as a premedicant and also for attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation with oral diazepam 0.2 mg/kg and placebo found that clonidine produced marked sedation and better anxiolysis as compared to Placebo but less sedation and same level of anxiolysis as compared to diazepam.[20]

Kumari I, Pathania VS in their study A prospective double blind placebo controlled trial of oral Gabapentin 900mg in attenuation of hemodynamic responses during laryngoscopy and tracheal intubation showed that gabapentin in this dose attenuated hemodynamic response to intubation significantly compared to placebo although the change in heart rate was not significant between both groups. [21]

IditMatot and co authors in their study The Effect of Clonidine Premedication on Hemodynamic Responses to Microlaryngoscopy and Rigid Bronchoscopy advocated that a dose of 300 micrograms clonidine blunted the hemodynamic response to

endoscopy. Ventricular arrhythmias were more frequent in patients who were not premedicated with clonidine. Two patients in the control group, but none in the clonidine group, had evidence of myocardial ischemia. [22]

Shivinder Singh and KapilArorain their study ofEffect of oral clonidine premedication on perioperative haemodynamic response and post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy concluded that the administration of oral clonidine 150 μg is a simple and cost effective form of premedication in patients undergoing laparoscopic cholecystectomy and results in improved perioperative haemodynamic stability and reduction in anaesthetic requirements. In addition, it also reduces the post-operative analgesic requirements. [23]

Talebi H and colleaguesin a prospective double blind randomised study, studied the Effects of oral Clonidine premedication on haemodynamic response to laryngoscopy and tracheal intubation on 274 ASA I and II subjects with age of 18 to 45 years scheduled for elective surgery under general anesthesia. They received oral clonidine (0.2 mg) or placebo as premedication 90-120 min before surgery. The Clonidine group showed a significant superiority over placebo in the prevention of increase in systolic blood pressure as well as heart rate over the intubation. A significant difference was observed in both heart rate and systolic blood pressures were significantly higher in Control group at three subsequent measurements following intubation suggesting that orally administered clonidine in preanesthetic period, provides more haemodynamic stability and attenuates the stress response to laryngoscopy and intubation. [24]

Marashi SM, Ghafari MH and Saliminia A compared oral Clonidine and Gabapentin for postoperative pain, its intensity, morphine consumption, nausea and vomiting. Their study demonstrated that oral premedication with Gabapentin significantly decreases the post-operative pain, morphine consumption, without any increase in PONV(post operative nausea vomiting). However, clonidine can only decrease post-operative pain without morphine consumption.[25]

Prabhakar H in 2007 conducted a study regarding the analgesic effects of preemptive gabapentin in patients undergoing surgery for brachial plexus injury and concluded that a single oral dose of gabapentin 800 mg, as preemptive analgesic in patients undergoing surgery for brachial plexus injury is found to be an effective adjunct to intraoperative and postoperative pain. Pain is reduced not only at rest but also during movement. [26]

Pandey CK and colleagues in 2006 conducted a study under title prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study and concluded that gabapentin effectively suppresses nausea and vomiting in laparoscopic cholecystectomy and post-operative rescue analgesic requirement. [27]

Kulka PJ and colleagues in a randomised control study, studied the dose response effects of intravenous clonidine 2,4 and 6 micrograms per kg body weight on stress response during induction of anaesthesia in patients undergoing CABG(coronary

artery bypass grafting) and found that clonidine 4µg/kg intravenous is the appropriate dose to attenuate stress response in CABG patients. [28]

Laurito C H, Baughman V L in a prospective randomised control study found that oral clonidine in a dose of 300 microgram given 90 minutes prior to laryngoscopy blunts the haemodynamic response to brief but not prolonged laryngoscopy .[29]

Review Of Anatomy Of Upper Airway[30]

The afferent pathway for reflex cardiovascular response to laryngoscopy and intubation is the sensory nerve supply to upper airway.

Laryngoscopy involves insertion of laryngoscope into right side of the mouth advancing forward pushing the tongue towards left and when the tip of the blade is at the valeculla (the space between base of tongue and pharyngeal surface of epiglottis) a forward and upward movement of the handle of the laryngoscope causes the epiglottis to move upwards like a trap door and vocal cords are visualised.

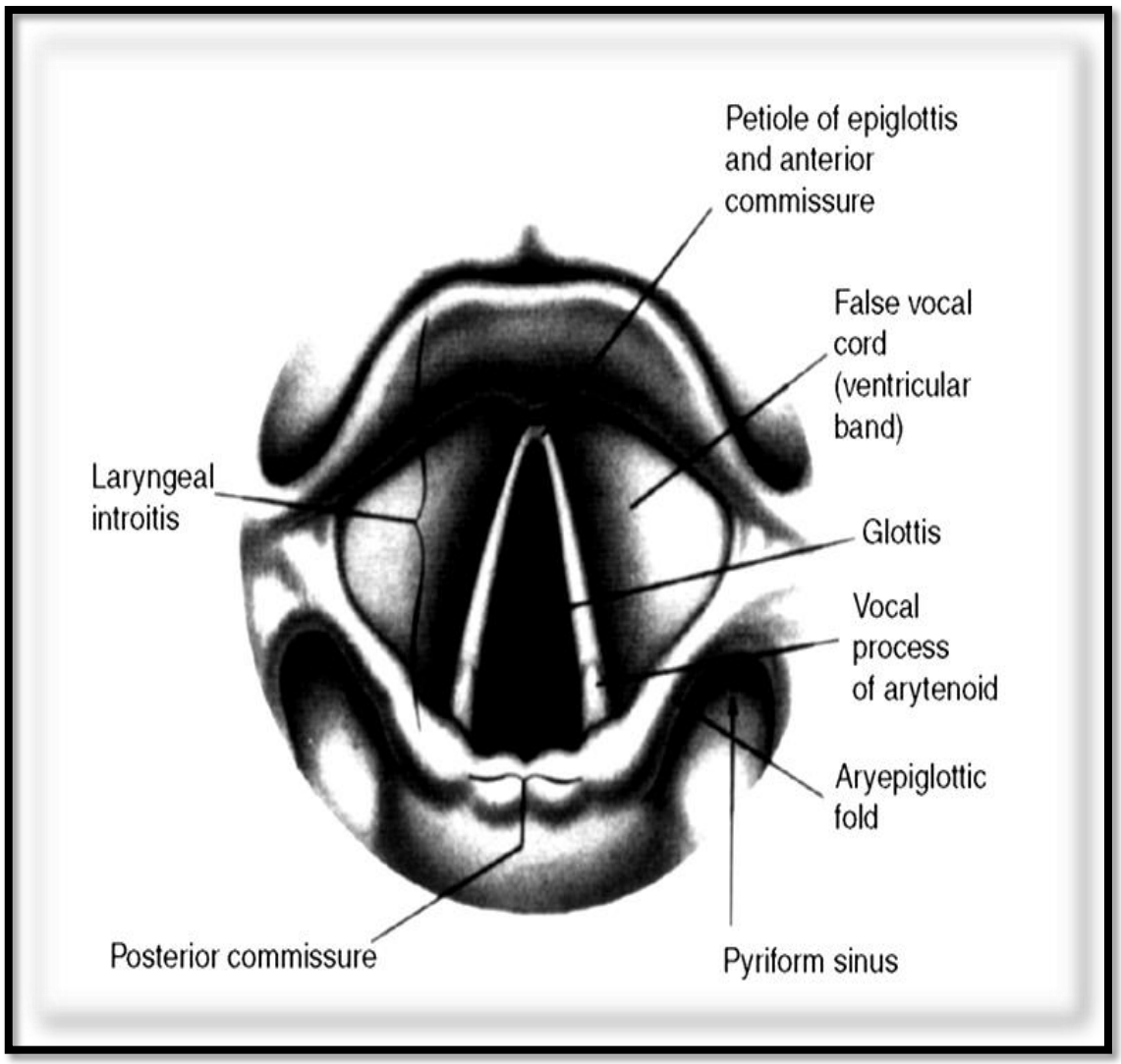
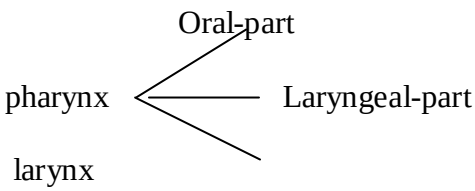


Figure 1- Laryngoscopic view of larynx

Upper airway includes the nasal cavity, oral cavity and



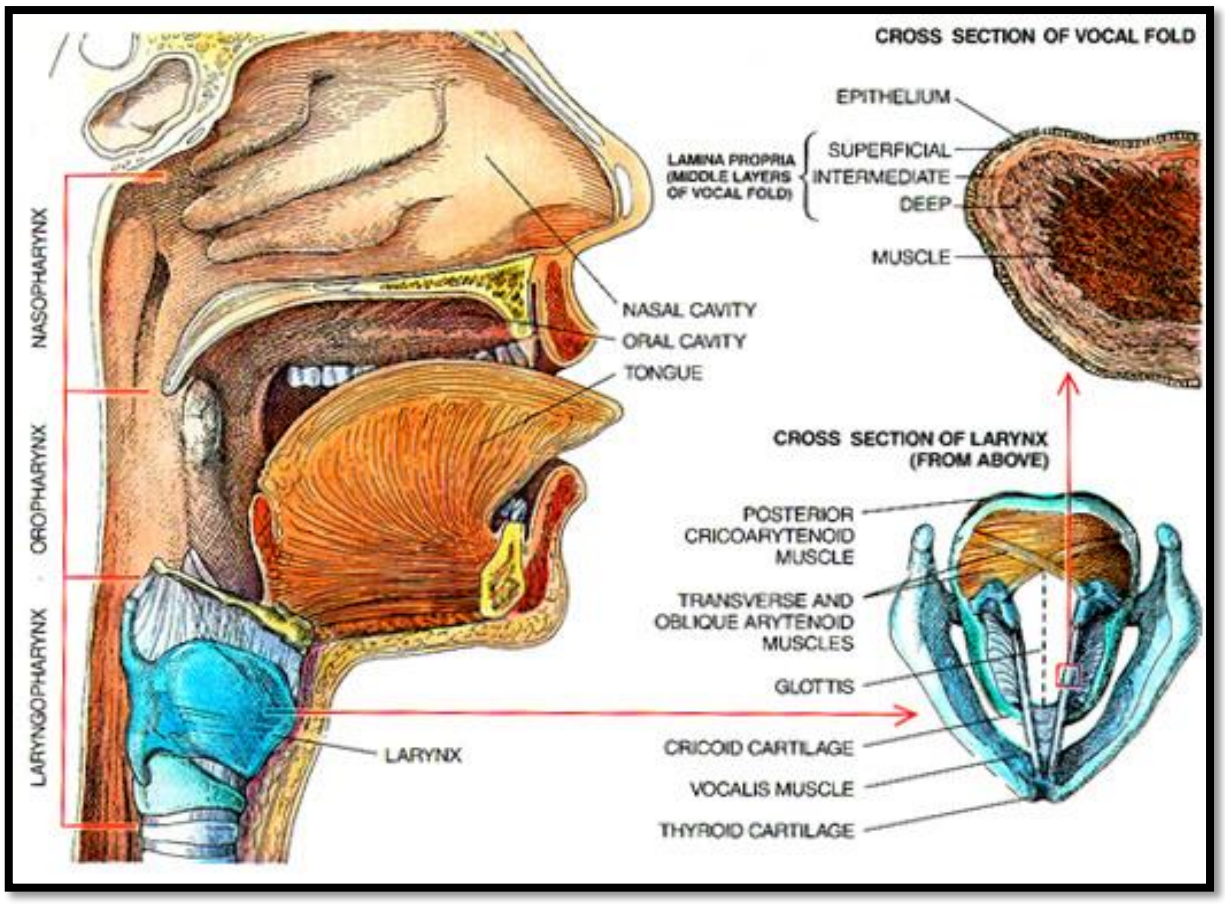


Figure 2- Anatomy of larynx

SENSORY NERVE SUPPLY OF UPPER AIRWAY

NASAL CAVITY

- Olfactory nerves arise from special olfactory cells present in the olfactory mucus membrane and relay in olfactory bulb.

- Nerves of ordinary sensation arise from branches of nasociliary nerve, a branch of (V1) trigeminal nerve and branches of maxillary division (V2) of trigeminal nerve.

- Sympathetic post ganglionic vasoconstrictor fibres from superior cervical ganglion.

- Para sympathetic post ganglionic secretomotor fibres from the pterygopalatine ganglion supply the nasal glands.

MUCOUS MEMBRANE OF ORAL CAVITY

- Roof of the mouth is supplied by the greater palatine and nasopalatine nerves branches of maxillary division of trigeminal nerve.

- Floor is supplied by the lingual nerve branch, mandibular division of trigeminal nerve.

- Cheek is supplied by buccal nerve, branch mandibular division of trigeminal nerve.

TONGUE

- Anterior 2/3rd by lingual nerve (general sensation) and chorda tympani (taste).

- Posterior 1/3rd by glossopharyngeal nerve for both general and taste sensation.

PALATE

- Hard and soft palates are innervated by greater and lesser palatine nerves, nasopalatine and glossopharyngeal nerves.

PHARYNX

- Nasal part by maxillary nerve (V2).

- Oral part by glossopharyngeal nerve.

- Laryngeal part by internal laryngeal branch of vagus nerve.

EPIGLOTTIS

- Anterior surface by glossopharyngeal nerve.
- Posterior surface by vagus nerve.

LARYNX

- Mucus membrane above vocal cords by internal laryngeal nerve.
- Mucus membrane below the vocal cords by recurrent laryngeal nerve.

PhysiologicalAnd Pathophysiological Response To Laryngoscopy And Intubation

Laryngoscopy, endotracheal intubation and other airway manipulations like suctioning, placement of Combitube and insertion of LMAs are noxious stimuli that induce profound changes in cardiovascular physiology, primarily through reflex responses.

Although these responses are of short duration and of little consequences in healthy individuals, serious complications may occur in patients with underlying coronary artery disease, reactive airways or in patients with intracranial pathology.[31]

Cardiovascular responses to noxious stimuli are initiated by proprioceptive receptors responding to tissue irritation in supra glottis, glottis and trachea. These proprioceptors are in close contact with airway mucosa. The glossopharyngeal and vagal afferent nerves transmit these impulses to brainstem, which in turn causes wide spread activation of sympathetic and parasympathetic nervous system.

Bradycardia seen in children during laryngoscopy and intubation is a result of reflex from an increase vagal tone at the sino atrial node. It is a monosynaptic response to the noxious stimuli.

In adults more common response is hypertension and tachycardia mediated by cardioaccelerator nerves and sympathetic ganglia. The response includes widespread release of norepinephrine from adrenergic nerve terminals and secretions from adrenal medulla. There is increased traffic of outflow in the sympathetic nervous system.[31]

The increase in blood pressure, heart rate, plasma epinephrine, norepinephrine and vasopressin concentrations are known to correlate with each other during laryngoscopy and intubation.

The most common adverse cardiovascular effect related to laryngoscopy and intubation is myocardial ischemia in patients with coronary artery disease. Two major determinants of myocardial oxygen demand are heart rate and blood pressure. The increase in myocardial oxygen demand created by hypertensive and tachycardic response to laryngoscopy and intubation must be met by an increase in flow of oxygenated blood through coronary circulation. However in patients with coronary artery disease the demand cannot be met and hence result in myocardial ischemia.[31]

PHARMACOLOGY OF CLONIDINE[32]

Clonidine, an imidazoline derivative, was synthesized in the early 1960s and was found to produce vasoconstriction which was mediated by α-receptors. It was developed in clinical use mainly as a nasal decongestant, in view of its vasoconstrictorproperties by $\alpha_1$agonist action. The centrally mediated α_2 agonistic action ofclonidine makes it a useful antihypertensive agent and has particular

relevance in theanaesthetic context. It was used in clinical practice in 1966 in Europe and later in theUnited States as an antihypertensive.

CHEMISTRY: $C_9H_9N_3Cl_2$ .HCl.

2,6-Dichloro-N-2-imidazolidinylidenebenzaminehydrochloride.

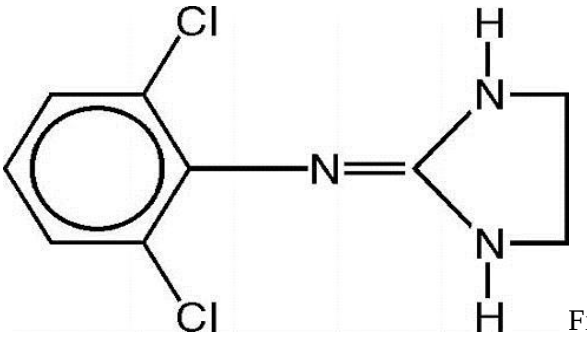


Figure 3- structure of clonidine

PHARMACOLOGY:

The α_2-Adrenergic receptor

Clonidine is a partial agonist at α-adrenoceptors both within the central nervous system and in the periphery. It is more specific for α_2-adrenoceptors than for α_1-adrenoceptors with a ratio of affinity of approximately 200:1.

Within the central nervous system α_2-adrenoceptors are located both presynaptically on terminals of neurons and postsynaptically on nor-adrenergic neurons. Clonidine acts at all central α_2-receptors, stimulation of which is associated with decreased neuronal excitability and inhibition of membrane bound adenylatecyclase. High concentrations of clonidine may stimulate central α_1-adrenoceptors enhancing neuronal excitability.

Stimulation of peripheral presynaptic α_2-adrenoceptors on post ganglionic noradrenergic or cholinergic neurons by clonidine contributes to reduced saliva flow, reduced intestinal motor activity, gastric acid secretion, and bradycardia.

Endocrine and metabolic effects apparently mediated by α_2-adrenoceptor stimulation are increased TSH and HGH secretion, decreased ACTH and ADH secretion, and

inhibition of glucose-stimulated insulin release. Clonidine inhibits insulin secretion from the pancreatic βcell possibly via anα_{2A} receptor.[33]

The pressor effect of high doses of clonidine is due to peripheral vasoconstriction mediated by stimulation of postsynaptic α_1 and $\alpha_2$adrenoceptors on vascular smooth muscle.

The imidazoline receptor:

Imidazoline receptors include three subtypes (I_1, I_2 and I_3) and are widely distributed in the body including the CNS.[34]

Clonidine as an imidazoline binds to these imidazoline receptors, in addition to its well-described binding to α_2-receptors.

Pharmacological Actions:

Cardiovascular Actions

The actions are classified as **peripheral and central**.

Effects on heart:

Clonidine inhibits norepinephrine release from the peripheral prejunctional nerveendings and causes bradycardia. There are no postjunctionalα_2 receptors inmyocardium. Hence a direct effect on heart is unlikely. It causes hypotension due tocentrally mediated reduction in sympathetic outflow. Clonidine exerts vagomimeticeffect on heart by stimulating nucleus tractussolitarius which can be attenuatedcompletely by highly selective muscarinic M_2 receptor antagonists.[35]

It can causebradycardia and reduction in cardiac output without affecting the cardiac contractilityand peripheral vascular resistance. It enhances the baroreflex sensitivity. In higherdoses it depresses the atrioventricular nodalconduction with slight prolongation ofP-R interval. It has antiarrhythmic action mediated via imidazoline receptors and vagus.

i. Effects on Coronary Vessels:

In vivo, clonidine causes coronary vasodilatation by releasing Endothelium DerivedRelaxing Factor (EDRF). It also enhances the vasodilatation caused by endogenousand exogenous adenosine. The vasoconstrictive action on proximal coronary bed isdue to predominance of α_2 adrenoreceptors causing direct vasoconstriction. Thiseffect is offset by the central reduction in sympathetic outflow.[36]

Endocrine And Metabolic Effects:

In patients with the usual low fasting plasma growth hormone (HGH) concentrations, clonidine acutely increases plasma HGH concentrations and chronically may be associated with increases of variable magnitude in basal HGH concentrations. With high basal HGH concentrations, clonidine acutely and chronically decreases HGH concentration.

Acute and chronic administration of clonidine reduces plasma ACTH and cortisol concentrations.[37]

There is no effect on the plasma concentrations of prolactin, FSH, or LH.

Clonidine also causes a small rise in blood glucose and a fall in plasma insulin normally. Both effects are inhibited by the peripheral α_2-antagonist MK-467.[38]

The effects of clonidine on carbohydrate metabolism appears to be variable. Some studies suggest that clonidine does not affect carbohydrate metabolism in diabetic or non-diabetic hypertensive patients[39]. Conversely, clonidine was associated with severe hypoglycemia in children when used as a provocative test for growth hormone deficiency. Studies have shown that clonidine administration in animals and man causes slight hyperglycemia, lipid mobilization and increase in growth hormone levels.[40]

Hyperglycemia due to by clonidine was reversed by infusions of the α-adrenergic blocking agent phentolamine and in the presence of α-blockade, clonidine had no effect on plasma glucose.[41]

Clonidine was reported to decrease glucose tolerance in maturity onset diabetics without any significant effect on glycemic control[42], and clonidine was also shown to favourably alter lipid profile. Clonidine appears to be promising in diabetic hypertensive patients.[43,44]

Actions On Gastrointestinal Tract

Clonidine may stimulate $\alpha_2$adrenoceptors on enterocytes thus promoting fluid and electrolyte absorption and inhibiting anion secretion. It may also modify intestinal motility and rectal sphincter tone. Because of these antidiarrhoeal properties, clonidine has been found to be of benefit in diabetic diarrhoea and in diabetic gastroparesis[45].

Other Actions

Clonidine decreases the body core temperature thresholds for vasoconstriction and shivering[46]. This action has been utilized during recovery from anaesthesia.

Pharmacokinetics:-

Clonidine is well absorbed after oral administration, and its bioavailability is nearly 100%, with peak concentrations in plasma and the maximal hypotensive effect being observed 1 to 3 hours after an oral dose. The elimination half-life of the drug ranges from 6 to 24 hours, with a mean of about 12 hours. Approximately half of the administered dose can be recovered unchanged in urine. There is good correlation between plasma concentrations of clonidine and its pharmacological effects. A transdermal delivery patch, an alternative to oral therapy permits continuous administration of clonidine. The drug is released at an approximately constant rate for a week, requiring 3 or 4 days to reach steady-state concentrations in plasma. When the

patch is removed, plasma concentration remain stable for about 8 hours and then decline gradually over a period of several days, this decrease in concentration is associated with a rise in blood pressure.Clonidine crosses the placenta and is distributed into breast milk.

DOSAGE:

Clonidine has been used in a wide dose range for various studies. The clinicallyeffective range is 2 to 5 µg/kg body weight for attenuation of hemodynamic responses to laryngoscopy and intubation.

ADVERSE EFFECTS:

The major adverse effects of clonidine are dry mouth and sedation occurring in atleast 50% of patients and may require drug discontinuation. However, they may diminish in intensity after several weeks of therapy. Sexual dysfunction may also occur. Constipation is also common. Marked bradycardia is observed in some patients.

Other adverse effects which have been reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, slight orthostatic hypotension, dry, itching or burning sensation in the eyeand transient abnormalities in liver function tests have been reported.

Symptoms of over dosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma.

Sudden withdrawal of clonidine may produce rebound hypertension.No teratogenicity, mutagenicity or carcinogenicity have been demonstrated with clonidine.[47]

PRECAUTIONS:

Clonidine should be used with caution in patients with cerebrovascular disease, ischemic heart disease including myocardial infarction[48], renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already receiving other antihypertensives such as guanethidine or reserpine.

Withdrawal of clonidine therapy should be gradual as sudden discontinuation may cause rebound hypertension.[49]

Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may occur. Clonidine hydrochloride has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

CONTRAINDICATIONS:-

• Disorders of cardiac pacemaker activity and conduction.

• Sino-atrial node disease (Sick sinus syndrome)

• Atrioventricular node disease.

DRUG INTERACTIONS:-

I. POTENTIALLY HAZARDOUS INTERACTIONS

- **Central nervous depressants**

Hypnosedatives, antihistamines and alcohol may cause excessive drowsiness in patients treated with clonidine.

- **β-Adrenoceptor antagonists**

In patients also receiving non-cardioselectiveβ-blockers, the rebound of blood pressure following clonidine-withdrawal may be more marked due to unopposed α-adrenoceptor mediated vasoconstriction[49].

- **Antipsychotics**

Acute severe hypotension has been observed following concomitant administration of clonidine and chlorpromazine or haloperidol.

II. OTHER SIGNIFICANT INTERACTIONS

- **Tricyclic and other antidepressants**

One double blind study has demonstrated attenuation of the hypotensive effect of clonidine by desipramine[50].

- **α-Adrenergic antagonists**

The effects of clonidine may be antagonized by centrally acting α-blockers such as phentolamine, tolazoline and phenoxybenzamine.

III. POTENTIALLY USEFUL INTERACTIONS

Diuretics and/or vasodilators may be used in combination with clonidine to enhance its hypotensive effects. Diuretics will counteract any tendency to fluid retention.

Clonidine may substitute for β-blockers in opposing the reflex cardiac stimulation following administration of vasodilators such as hydralazine or nifedipine.[51]

Therapeutic Uses

- **In Hypertension**

Clonidine, an imidazoline antihypertensive is used in the management of hypertension[52], including hypertensive crises, although other drugs with fewer adverse effects are now generally preferred. It appears to act centrally to reduce sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart

rate. It also acts peripherally and this activity may be responsible for the transient increase in blood pressure seen during rapid i.v. administration as well as, contributing to the hypotensive effect during chronic administration.

In hypertension, the usual initial dose of clonidine hydrochloride is 50-100 micrograms three times daily orally, increased every second or third day according to response; the usual maintenance dose is 300 to 1200 micrograms daily but doses of 1800 micrograms or more daily may sometimes be required.

Clonidine may also be given by transdermal delivery systems that are applied once a week and deliver 100 to 300 micrograms of clonidine base daily at a constant rate.

Clonidine hydrochloride may be given by slow i.v. injection over 10 to 15 minutes in hypertensive crises, usually in doses of 150 to 300 micrograms.

- **Anxiety Disorders**

Clonidine might be useful in patients unresponsive to standard treatments, based on benefits obtained in small number of patients with panic attacks[53], and post-traumatic stress disorders.[54]

- **Glaucoma**

Topical solutions of clonidine significantly reduced intraocular pressure in patients with open-angle glaucoma.[55]Apraclonidine is in use now.

- **Psychiatric Disorders**

Clonidine is reported to be effective in the treatment of acute mania, in combination with lithium and antipsychotic drugs.[56]

- **Diarrhoea**

Clonidine, because of its antidiarrhoeal properties is used in diarrhoea, most commonly in diabetic diarrhoea and also in diabetic gastroparesis.[57]

- **ADHD (Attention Deficit Hyperactivity Disorder)**

Clonidine has been tried mainly as an adjuvant to a central stimulant.[58]

- **Menopausal Disorders**

Clonidine has been of some use in countering vasomotor symptoms in patients who cannot receive HRT, and also to control hot flushes[59] in women receiving tamoxifen. It is best reserved for women who are also hypertensive.

- **Premedication**

It has been used pre-operatively for its sedative, anxiolytic and analgesic effects and to provide hemodynamic stability and reduce anaesthetic requirements, and to reduce post-operative vomiting in children[60] and in women.[61]

- **Pheochromocytoma**

Since clonidine acts centrally to suppress catecholamine release, it may be used in the diagnosis of pheochromocytoma.[62]

- **Shivering**

Clonidine's central and peripheral effects could account for its antishivering activity, and thus has been used to stop shivering after general anaesthesia[63] or epidural anaesthesia.

- **Substance Dependance**

Alcohol: Clonidine has been used sometimes to produce benefit[64], but should not be used as sole therapy, as it does not have any effect on convulsions and delirium tremens.

Opioid Analgesics: Clonidine has been used with naltrexone to shorten the withdrawal syndrome[65], and it has also been used in the management of neonatal abstinence syndrome in infants born to opioid-addicted mothers maintained on methadone.[66]

Smoking: Clonidine is usually reserved for second-line treatment[67] in those who experience severe agitation and anxiety when stopping smoking.

- **Pain**

Clonidine has been tried by the epidural or intrathecal routes, alone or as an adjunct to opioids, and local anaesthetics to produce effective analgesia in post-operative pain[68], labour pain[69], neuropathic pain and chronic pain due to cancer.

- **Tourette's Syndrome**

Clonidine by its suppressant action on central noradrenergic activity and other neurochemical system, can be effective as first-line treatment in patients with mild to moderate symptoms.[70]

PREPARATIONS

Oral forms- Catapres tablets, Dixarit tablets, Catapres PL perlongets

25µg, 100µg, 200µg, 250µg.

Transdermal form-Catapres TTS: are transdermal patches delivering clonidine100µg, 200µg or 300µg daily for 1 week.

Parenteral form

Catapres injection: 150µg ml-1 in 1 ampoule, intended for slow i.v. injection.

Clonidine hydrochloride is also available in combination with chlorthalidone, triamterene, hydrochlorothiazide, bencyclane, fumarate, or cyclothiazide.

PHARMACOLOGY OF GABAPENTIN[71]

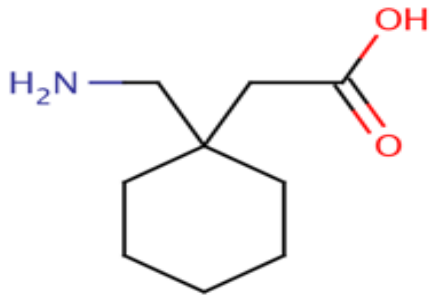


Figure 4- Structure of Gabapentin

Gabapentin is an antiseizure drug that consists of a GABA molecule covalently bound to a lipophillic cyclohexane ring. Gabapentin was designed to be a centrally active GABA agonist.

Chemistry-

Gabapentin (1-aminomethyl-cyclohexaneacetic acid)

Formula - $C_9H_{17}NO_2$

Gary and Larry Mellick published the first reports of gabapentin treatment of neuropathic pain and reflex sympathetic dystrophy in May 1995.[72]

Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. High performance liquid chromatography and gas chromatography can be used for drug assay in plasma and urine.

MECHANISM OF ACTION

The mechanism by which Gabapentinexerts its analgesicaction is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, Gabapentinprevents pain-related responses in several models of neuropathic pain in rats or mice.[73]Gabapentin is structurally related to

the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding.[74] *In vitro* studies with radiolabelled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels.[75]

ANTI-NOCICEPTIVE MECHANISMS-

A number of mechanisms may be involved in the actions of gabapentin.[76] Possible pharmacologic targets of Gabapentinare selective activation of the heterodimeric $GABA_B$ receptors which consist of $GABA_{B1a}$ and $GABA_{B2}$ subunits; enhancement of the N-methyl-D-aspartate (NMDA) current at GABAergic interneurons;[77]blocking a-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord; binding to the L-α-amino acid transporter; activatingadenosine triphosphate sensitive K+ (K_{ATP}) channels; activating hyperpolarization-activated cationcurrent (Ih) channels[78]and modulating Ca_2^+ current by selectivelybinding to gabapentin (a radioligand), the a2δ subunit of voltage-dependent Ca_2^+channels (VGCCs).Currently, VGCC is the most likely anti-nociceptive targetof gabapentin.[79]The proposed consequence of gabapentin binding to the a2δ subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability.[80,81]

Gabapentin has been shown to inhibit the evoked release of Glutamate,Aspartate, substance P, and Calcitonin gene-related peptide (CGRP) from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal a2 adrenergic receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to a2δ

interaction.[82]However, functional correlates of gabapentin binding, if any, remain to be elucidated.

PHARMACOKINETICS AND DRUG METABOLISM[83,84]

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

***Oral Bioavailability*:** Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin.

***Distribution*:** Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD). After ingestion of a single 300 mg capsule, peak plasma concentrations (Cmax) of 2.7 µg /ml are achieved within 2–3 hours. Concentrations of gabapentin in cerebrospinal fluid are approximately 5–35% of those in plasma, whereas concentrations in brain tissue are approximately 80% of those in plasma.

***Elimination*:** Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing.Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended.[85]

Action on nervous system:

Gabapentin produces analgesia, anxiolysis& sedation.It is proposed that it increases the concentration & rate of synthesis of GABA in brain.

Formulation& routes of administration :

Gabapentin is currently not available parenterally. It is available in tablet & capsule form in the strength of 100,300, 400mg& 600mg usually in combination with methylcobolamin. ('Movapentin', 'Neurontin' 'Gabalin')

Clinical uses of Gabapentin

- Non anaesthetic and
- Anaesthetic

Non anaesthetic

- **As an anti-epileptic[86] :** Gabapentin is effective as an adjunct against partial seizures and generalized tonic- clonic seizures at dosages that range upto 2400mg/day. Double-blind placebo-controlled trials of adults with refractory partial seizures demonstrated that addition of gabapentin to other antiseizure drugs was superior to placebo (Sivenius*et al.*, 1991). A double-blind study of gabapentin (900 or 1800 mg/day) monotherapy disclosed that gabapentin was equivalent to carbamazepine (600 mg/day) for newly diagnosed partial or generalized epilepsy (Chadwick *et al.*, 1998).
- In **psychiatric patients** with comorbid anxiety related disorders, Gabapentin has long term anti- anxiety&hypnotic effects .[87]

- To decrease hot flushes in post-menopausal women.

Anaesthetic Uses Of Gabapentin :

- **In The Treatment Of Neuropathic Pain:**

Gabapentin can be used for the symptomatic treatment of painful diabetic neuropathy, as an adjunct to opioid analgesia for neuropathic cancer pain, for the treatment of post herpetic neuralgia, trigeminal neuralgia, chronic regional pain syndrome, HIV related neuropathy, headache post poliomyelitis neuropathy & other chronic pain states. 30-1200mg three times daily is the recommended dose for neuropathic pain.[88]

- **For Post Operative Analgesia[89]:**

Doses ranging from 300-1200mg given orally 1-2hrs before surgery have been found to be effective in reducing post operative opioid consumption in the first 24hrs after surgery & to a lesser extent in reducing pain scores.[90] 1200mg oral gabapentin given 1 hr before ambulatory ENT surgery done under Local Anesthesia& Monitored AnesthesiaCare provides significant analgesia.

Perioperative oral Gabapentin is a useful adjunct for the management of postoperative pain that provides analgesia through a different mechanism than opioids & other analgesics thus making it a reasonable addition to a multimodal analgesic treatment plan.[91,92]

- **As a pre emptive analgesic:**

Gabapentin elevates pain threshold & prevents acute nociceptive & inflammatory pain especially when given before trauma. Severalworkers have found that 300-1200mg oral gabapentin given 1 hr before surgical stimulus significantly reduces the incidence of pain &post operative opioid consumption without significant side effects.[93]In infraumbilical surgery, in absence of opioid or non opioid analgesics, pre

operativeGabapentin prolongs the analgesic effects of spinal analgesia & reduces the doses of peri operative analgesics.[94,95]

- **To attenuate haemodynamic response to direct laryngoscopy and endotracheal intubation**[96] :

Gabapentin 1-2 hrs before surgery effectively attenuates the increase in MAP & IOP in the first 10 min of laryngoscopy & endotracheal intubation. The mechanism is unknown. It inhibits membrane VGCCs, thus acting like a calcium channel blocker.

- **For pre operativeanxiolysis:**

Gabapentin pretreatment has been reported to produce significantly lower pre operative VAS anxiety scores and to thus allay pre-operative anxiety.[96]

- **Prevention of nausea & vomiting :**

600mg oralgabapentin 2 hrs before surgery effectively suppressesnausea&vomiting eg: in laparoscopic cholecystectomy.Gabapentin is also effective in reducing acute& delayedonset nausea & vomiting in patients on chemotherapyby mitigating tachykinin neurotransmitter activity.[97]

- **Prevention of postoperative delirium :**

The incidence of postoperative delirium has been found to be less in patients on peri operative Gabapentin. The mechanism is unknown and may be related to the opioid sparing effect of Gabapentin.[98]

- **Preventionofchronicpostsurgicalpain(CPSP):**

The effective treatment of acute pain is usually not associated with the prevention of chronic pain. CPSPis particularly common after limb amputation, inguinal hernia

repair, breast surgery & thoracotomy.[99]Peri operative Gabapentin (starting day before surgery & continued for 3-30 days post op) with or without combining with local wound infiltration of local anaesthetic like Ropivacaine / EMLA cream prevents the development of CPSP after limb amputation, breast &abdominal surgeries.[100]

DRUG INTERACTIONS[101]

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly co-administered antiepileptic drugs.

***Phenytoin*:** In a study of Neurontin in epileptic patients maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

***Carbamazepine*:** Steady-state trough plasma carbamazepine concentrations were not affected by concomitant gabapentin administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

***Valproic Acid*:** The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

***Phenobarbital*:** Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin are identical whether the drugs are administered alone or together.

***Morphine*:** A literature article reported that when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg Neurontin capsule

mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine .Morphine pharmacokinetic parameter values were not affected by administration of Neurontin 2 hours after morphine.

***Cimetidine*:** cimetidine appears to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function which is not expected to be of clinical importance.

Overdose[102]

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxialabored breathing ptosis , sedation, hypoactivity, or excitation.

Acute oral overdoses of Neurontin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis .

Side effects[103] **:**

Include dizziness (10.9%), somnolence (15.2%), nausea(3.2%), ataxia(2.6%), tremor, asthenia(6%),weight gain (2.6%), amblyopia (2.1%). These effects usually are mild to moderate in severity but resolve within 2 weeks of onset during continued treatment. Withdrawal symptoms may occur after abrupt discontinuation of high dose Gabapentin.

MATERIALS AND METHODS

The study was conducted at R.L .Jalappa Hospital and Research Centre, Tamaka, Kolar, on patients admitted for elective surgeries under general anaesthesia .

Sixty patients of ASA grade 1 and 2 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for the study.Patients were randomly divided on an alternative basisinto two groups of 30 each.

The study was conducted after obtaining ethical committee clearance and informed written consent was taken from patients in both the groups. The study design was randomized and double blinded.

All patients were examined a day before surgery. All were kept fasting overnight after 10:00pm and received tab. Diazepam 10mg orally and tab. Rantidine 150 mg as premedication on the night before surgery. On the morning of surgerythe study medications were given orally with sips of water 2 hour preoperatively by a staff nurse who was not involved in the study.

Group "C" received - 200µg clonidine .

Group "G" received- 900mg gabapentin .

Baseline parameters like pulse rate and systolic blood pressure, diastolic blood pressure, mean blood pressure , oxygen saturation and ECG were recorded, intravenous line were secured and all were given intravenous fluids 5 ml/kg.Temperature and urine output monitoring with an indwelling catheter were initiated in the operation theatre.

The level of sedation wasassessed by four point score described by Chernik et al.

Grade 0- patient wide awake.

Grade 1-patient is sleeping comfortably but responding to verbal commands.

Grade 2-deep sleep but arousable.

Grade 3-deep sleep, unarousable.

After 3 mins of pre-oxygenation with 100% oxygen , pre medication was done with 5 µg/kg of i.vglycopyrolate. 2.5µg/kg i.v Fentanyl wasgiven for analgesia. Patient wasinduced with i.vThiopentone 5 mg/kg followed by i.vsuxamethonium 2 mg/kg for intubation. Care was taken to note that the time taken for laryngoscopy was less than 15 seconds in all the patients. Anaesthesia was maintained with N_2O+O_2+Isoflurane(0.6-1%). Muscle relaxation was achieved with i.vVecuronium 0.1mg/kg(loading dose) and 0.02 mg/kg (maintenance dose) later.

The baseline heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was taken as 0 minute value. Thereafter the heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were recorded at 1,3,5 and 10 minutes after endotracheal intubation.Any episode of bradycardia (HR<53) was treated by injection Atropine 0.6mg.

INCLUSION CRITERIA:

Sixty patients of ASA Grade 1 and 2 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for study.

EXCLUSION CRITERIA

1) Patients belonging to ASA Grade 3 and above.

2) Patients physically dependant on narcotics.

3) Patients with history of drug allergy to clonidine or gabapentin.

4) History of cerebrovascular, neurologic, respiratory, Ischaemic heart disease (history of angina, previous Myocardial Infarction.

5) Renal and hepatic dysfunction.

6) Head injury cases and patients with difficult airways.

7) Patients with hypertension ,pheochromocytoma and diabetes mellitus.

8) Patients on beta blockers, anti-depressants, anti anxiety, anti convulsant or anti-psychotics.

The study required the following investigations:

Complete haemogram.

Bleeding time and clotting time.

Random blood sugar.

Blood urea and serum creatinine.

Serum electrolytes.

Urine analysis for sugar, albumin and microscopy.

ECG and chest X-ray.

STATISTICAL ANALYSIS

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and

results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups

Standard deviation: $SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables **.**

RESULTS

Study Design: A randomised prospective Comparative two groups study with 60 patients, randomized in to two groups, 30 in Group G (Gabapentin) and 30 in Group C(Clonidine) was undertaken to study the Hemodynamic Responses To Laryngoscopy And Tracheal Intubation "

Table 1: Age distribution of patients studied

Age in years	**Group G**		**Group C**	
	No	**%**	**No**	**%**
18-20	2	6.7	3	10.0
21-30	14	46.7	10	33.3
31-40	9	30.0	9	30.0
41-50	5	16.7	8	26.7
>50	0	0.0	0	0
Total	30	100.0	30	100.0
Mean ± SD	32.37±8.77		34.40±9.84	

Samples are age matched with p= 0.402

GRAPH 1

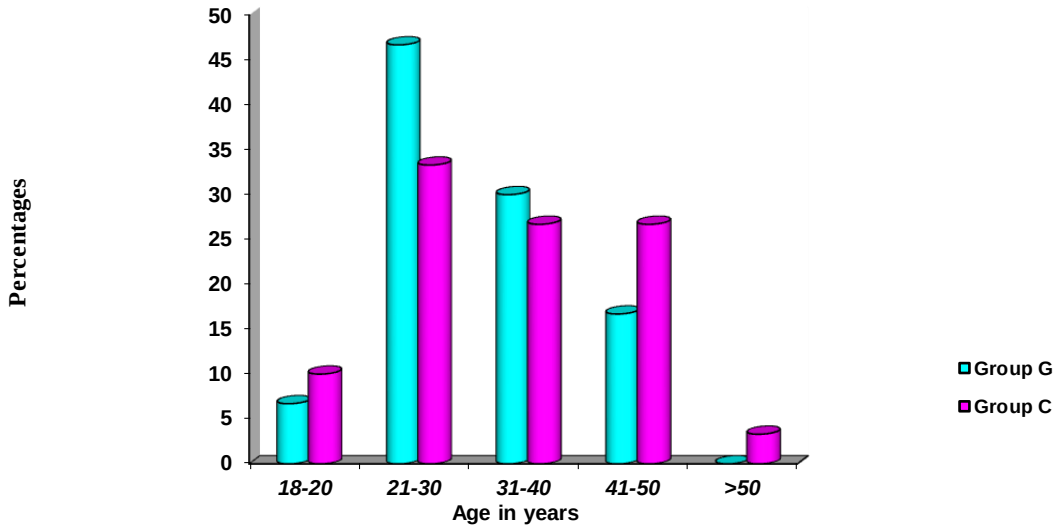


Table 2: Gender distribution of patients studied

Gender	Group G		Group C	
	No	%	No	%
Male	14	46.7	9	30.0
Female	16	53.3	21	70.0
Total	30	100.0	30	100.0

Samples are gender matched with p = 0.288

GRAPH 2

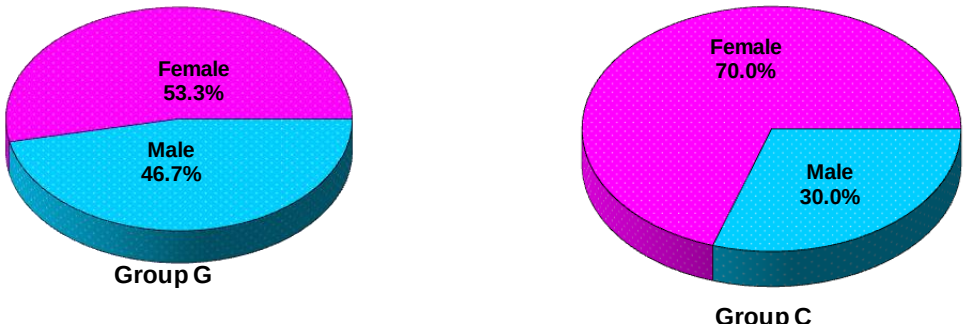
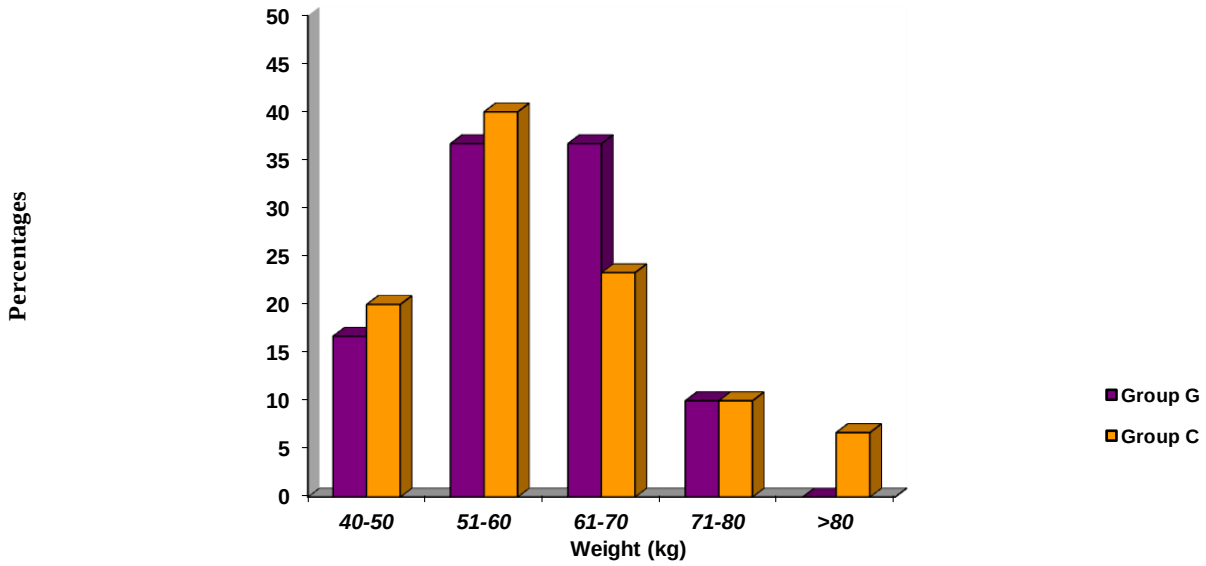


Table 3: Weight (kg) distribution of patients studied

Weight (kg)	Group G		Group C	
	No	%	No	%
40-50	5	16.7	6	20.0
51-60	11	36.7	12	40.0
61-70	11	36.7	7	23.3
71-80	3	10.0	3	10.0
>80	0	0.0	2	6.7
Total	30	100.0	30	100.0
Mean ± SD	59.37±9.46		61.10±11.05	

Weight distribution is statistically similar in two groups with p = 0.517

GRAPH 3



COMPARISON OF BASIC CLINICAL CHARACTERISTICS (AGE, GENDER AND WEIGHT)

The mean values and standard deviation of age in the two groups G and C were 32.37±8.77 and 34.40±9.84 respectively (P>0.05).

The male to female ratios in group G and group C were 14:16 and 9:21 respectively (P>0.05).

The mean values and standard deviation of weight in group G and group C were 59.37±9.46 and 61.10±11.05 (P>0.05).

We conclude that the sample studied are age, gender and weight matched.

Table 4: Comparison of heart rate (beats per minute) of two groups of patients studied

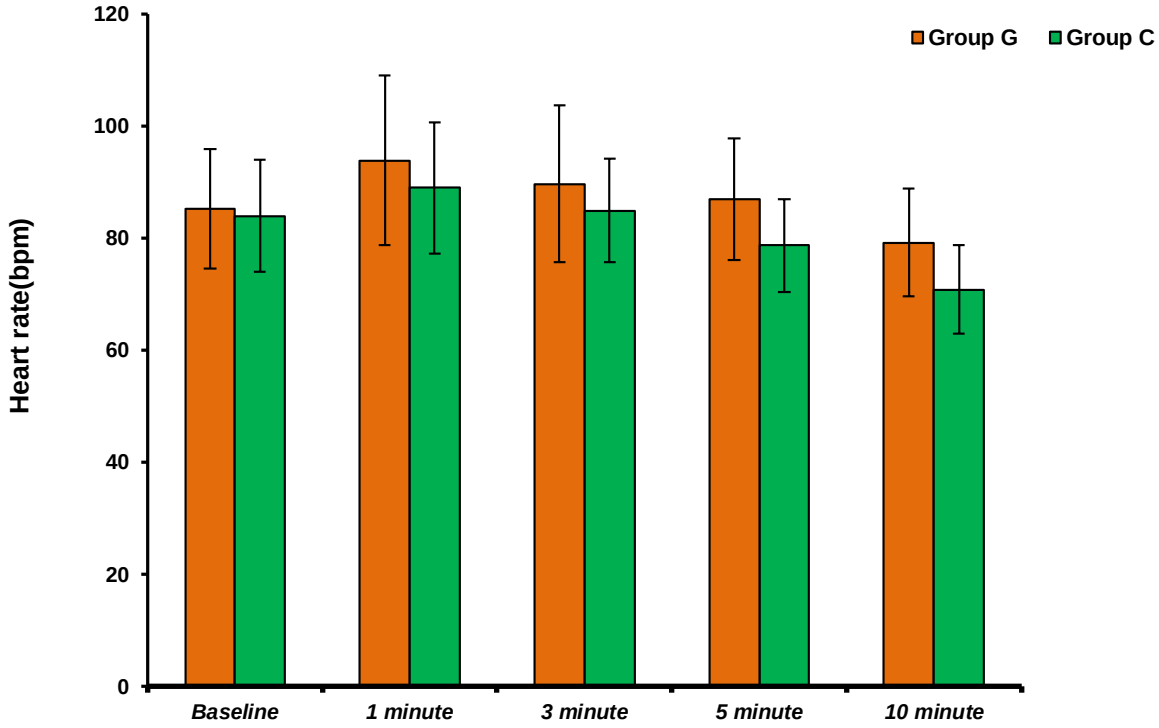
Heart rate(bpm)	**Group G**	**Group C**	**P value**
Baseline	85.30±10.72	84.03±10.06	0.639
1 minute	93.93±15.08	89.00±11.69	0.162
3 minutes	89.73±14.05	84.97±9.17	0.125
5 minutes	86.93±10.83	78.73±8.27	0.002**
10 minutes	79.27±9.66	70.87±7.87	<0.001**

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01<P ≤ 0.05)

** Strongly significant (P value: P≤0.01)

GRAPH4A



GRAPH4B

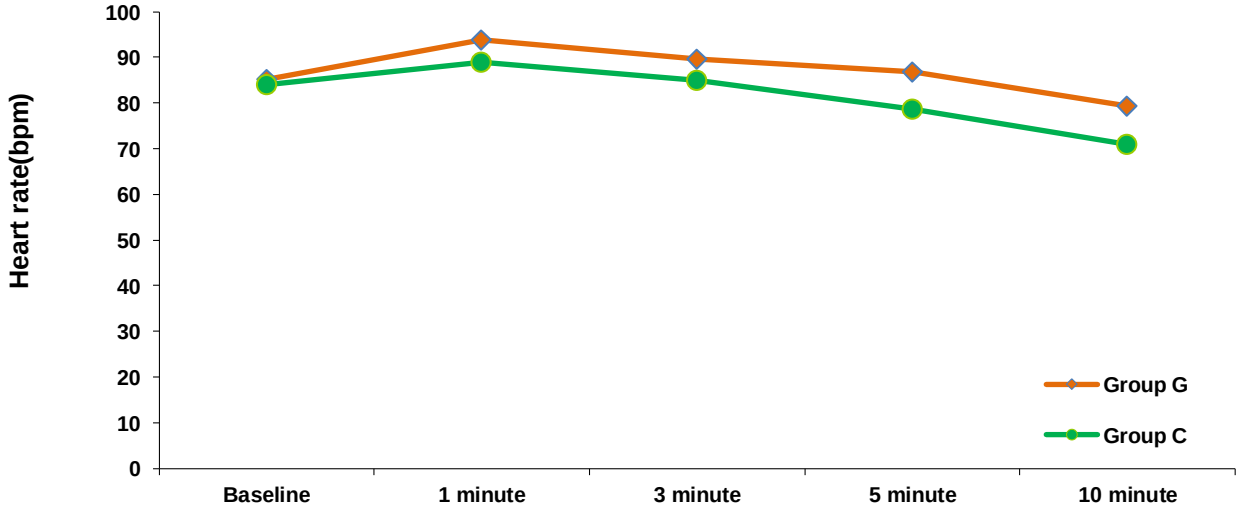


Table 4 and Graph 4A and 4B

COMPARISON OF HEART RATE IN THE TWO GROUPS:

GROUP G

Gabapentin group showed a mean baseline heart rate and standard deviation of 85.30±10.72. At 1 minute, 3 minute, 5 minute and 10 minute interval the increase in mean heart rate were 93.93±15.08, 89.73±14.05, 86.93±10.83 and 79.27±9.66 respectively.

Group C

Clonidine group showed a mean baseline heart rate and standard deviation of 84.03±10.06. At 1 minute, 3 minute, 5 minute and 10 minute interval the mean heart rate were 89.00±11.69, 84.97±9.17, 78.73±8.27 and 70.87±7.87respectively.

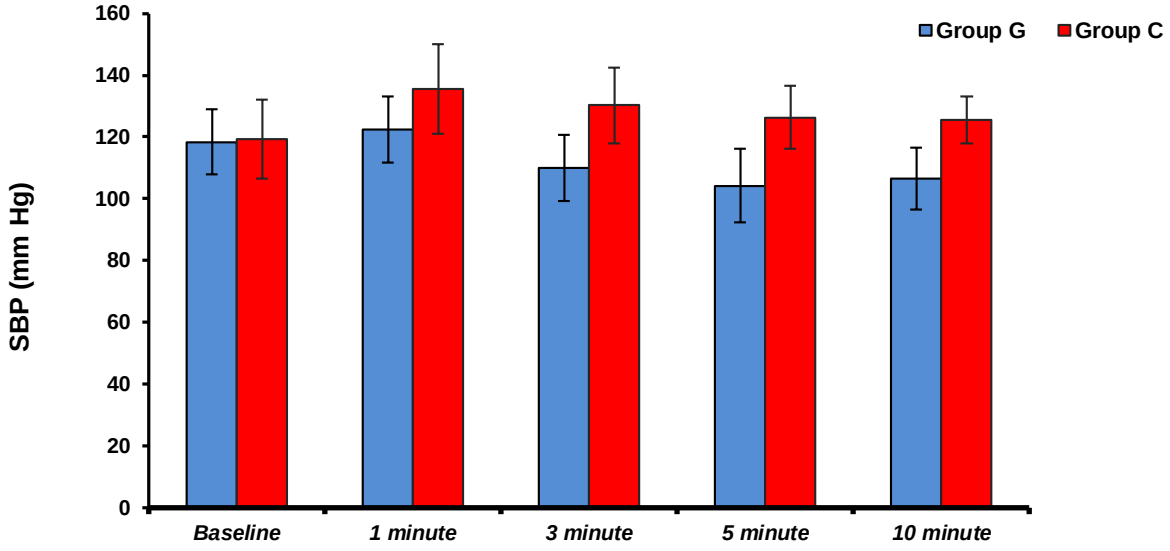
INTER GROUP COMPARISON

At 5 and 10 minutes heart rate response to laryngoscopy and intubation in the clonidine group is clinically lesser than gabapentin group and statistically highly significant ($p=0.002$ at 5 minute and $P<0.001$ at 10 minutes). The fall to baseline value in the Gabapentin group was at 5^{th} minute and in Clonidine group at 3^{rd} minute and this indicates Clonidine group showed earlier recovery to baseline values compared to Gabapentin group.

Table 5: Comparison of systolic blood pressure(mmHg) of two groups

SBP (mm Hg)	Group G	Group C	P value
Baseline	118.37±10.47	119.30±12.65	0.180
1 minute	122.47±10.63	135.63±14.47	<0.001**
3 minutes	110.03±10.66	130.23±12.17	<0.001**
5 minutes	104.20±11.87	126.37±10.21	<0.001**
10 minutes	106.53±9.85	125.47±7.59	<0.001**

GRAPH 5A



GRAPH 5B

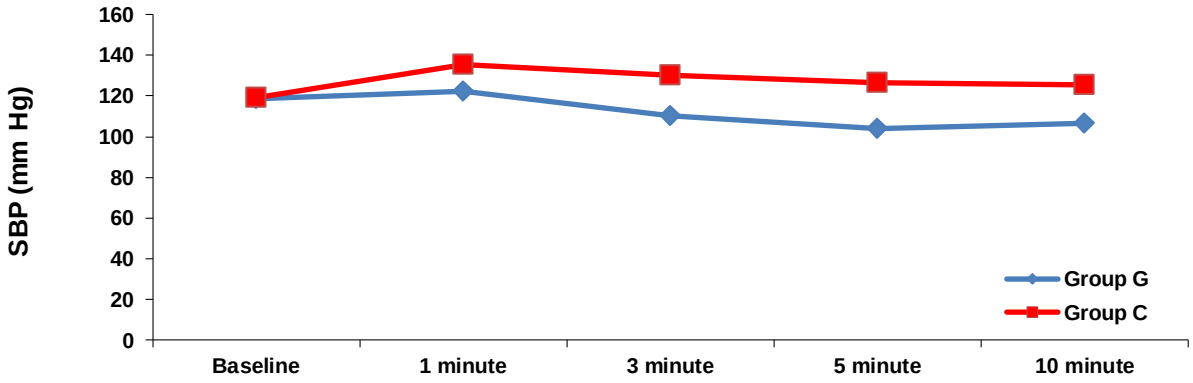


Table 5 and Graph 5A and 5B

COMPARISON OF SYSTOLIC BLOOD PRESSURE

GROUP G

The baseline mean and standard deviation of systolic blood pressure in group G was 118.37±10.47. The mean systolic blood pressures were 122.47±10.63, 110.03±10.66, 104.20±11.87 and 106.53±9.85 at 1minute, 3 minute, 5 minute and 10 minute intervals respectively from onset of laryngoscopy.

GROUP C

The baseline mean and standard deviation of systolic blood pressure in group C was 119.30±12.65. The mean systolic blood pressures were 135.63±14.47, 130.23±12.17, 126.37±10.21 and 125.47±7.59 at 1 minute, 3 minute, 5 minute and 10 minute intervals respectively from onset of laryngoscopy.

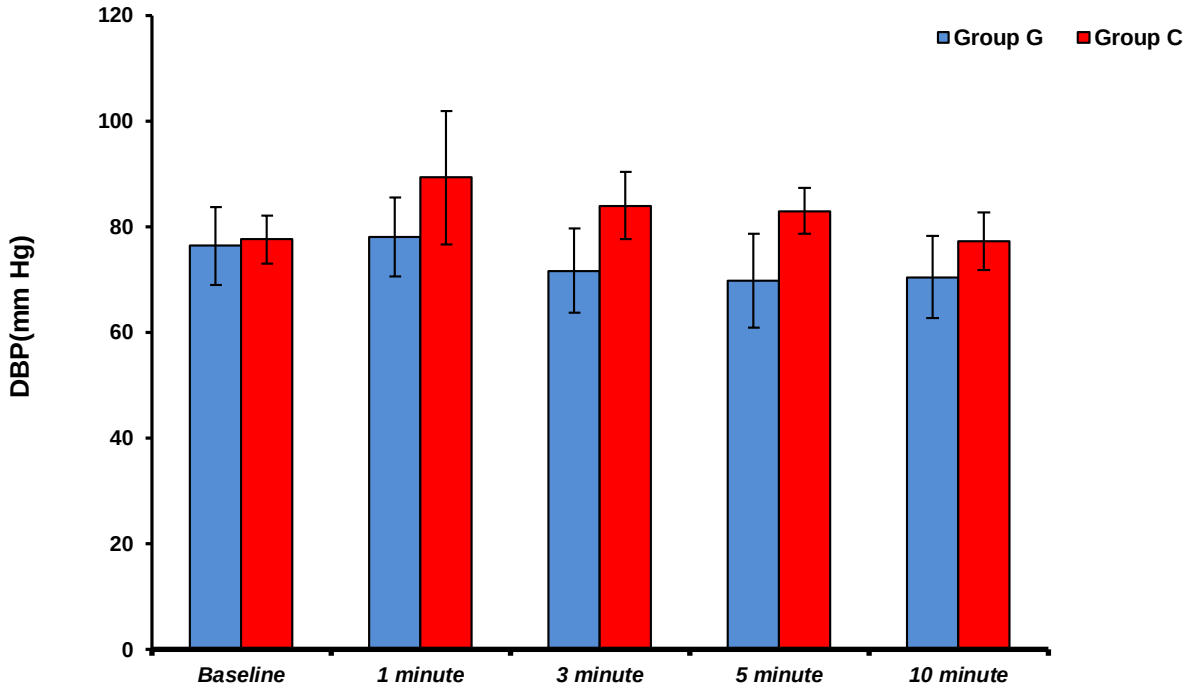
INTER GROUP COMPARISON

The mean systolic blood pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval is clinically lesser in Gabapentin group than in the Clonidine group. At 1, 3 and 5 minutes p value was <0.001. and is statistically highly significant indicating Gabapentin group attenuates the systolic blood pressure response to laryngoscopy and intubation better compared to group Clonidine .

Table 6: Comparison of diastolic blood pressure (mmHg) of two groups

DBP(mm Hg)	Group G	Group C	P value
Baseline	76.40±7.38	77.57±4.54	0.251
1 minute	80.10±7.45	89.30±12.58	<0.001**
3 minutes	71.63±7.97	83.93±6.37	<0.001**
5 minutes	69.73±8.91	82.93±4.32	<0.001**
10 minutes	70.47±7.79	77.20±5.49	<0.001**

GRAPH 6A



GRAPH 6B

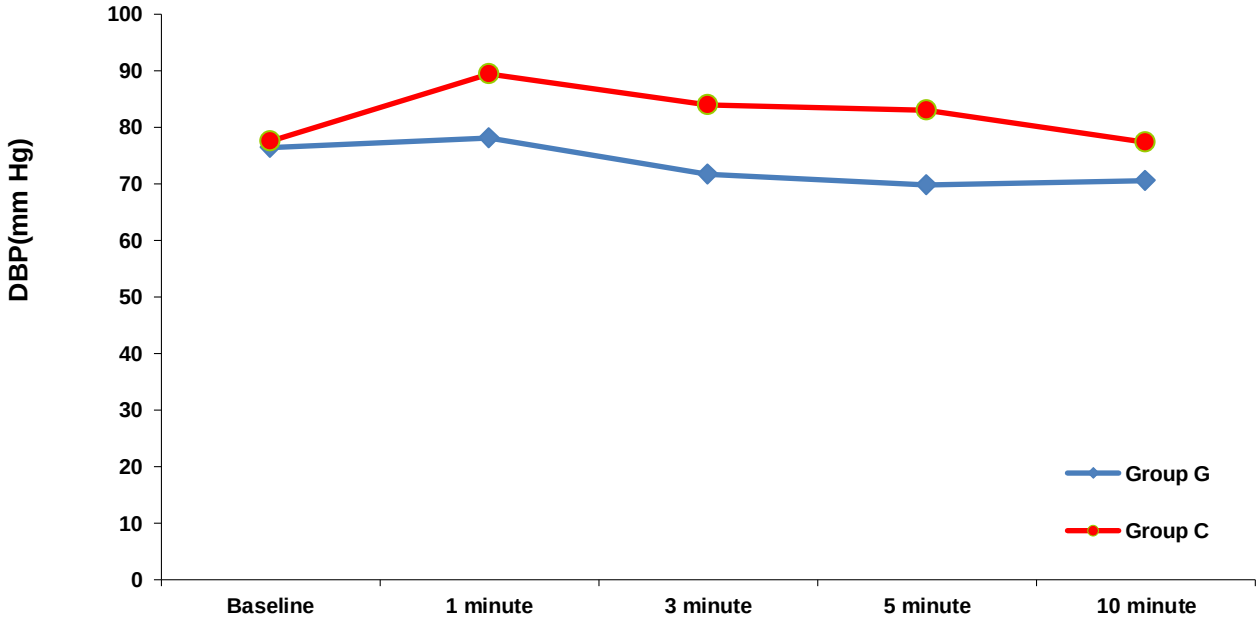


Table 6 and Graph 6a and 6b

Comparison of Diastolic Blood Pressure

GROUP G

The baseline mean and standard deviation of diastolic blood pressure in group G was 76.40±7.38. The mean diastolic blood pressures were 78.10±7.45, 71.63±7.97, 69.73±8.91 and 70.47±7.79 at 1 minute,3 minute, 5 minute and 10 minute intervals respectively(diastolic arterial pressure fell below the baseline value at 3,5 and 10 minutes).

GROUP C

The baseline mean and standard deviation of diastolic blood pressure in group C was 77.57±4.54. The mean diastolic blood pressureswere 89.30±12.58, 83.93±6.37, 82.93±4.32 and 77.20±5.49 at 1 minute,3 minute, 5 minute and 10 minute intervals respectively.

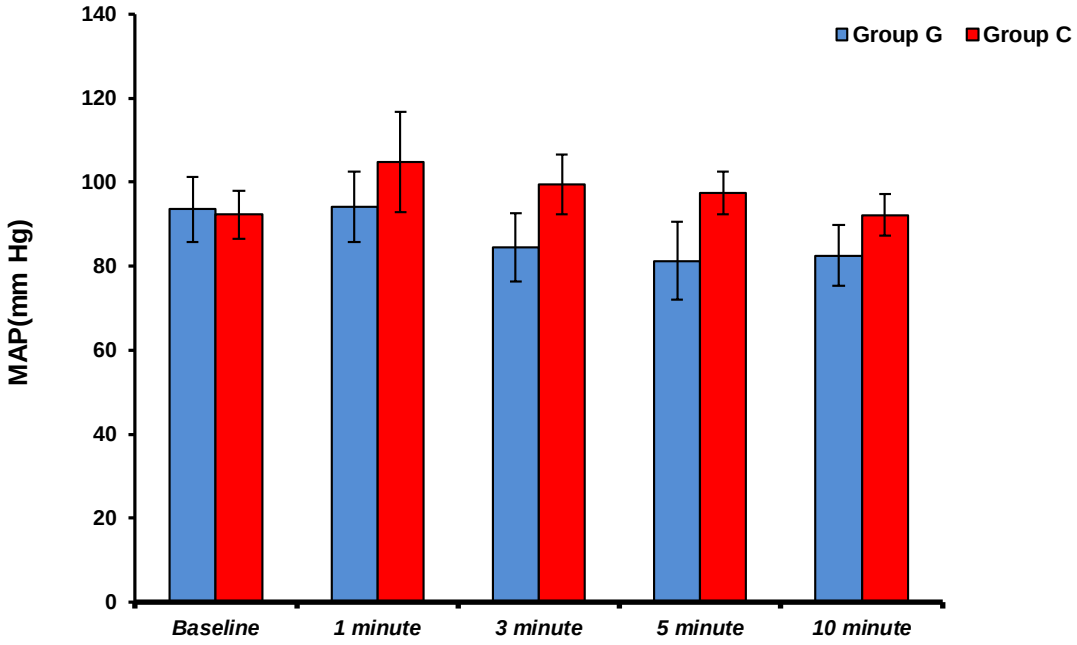
INTER GROUP COMPARISON

The mean diastolic blood pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval is clinically lesser in Gabapentin group than in the Clonidine group. At 1, 3 and 5 and 10 minutes p value was <0.001 and is statistically highly significant indicating Gabapentin group attenuates the diastolic blood pressure response to laryngoscopy and intubation better compared to group Clonidine .

Table 7: Comparison of MAP (mmHg) of two groups of patients studied

MAP(mm Hg)	Group G	Group C	P value
Baseline	93.49±7.69	92.26±5.75	0.485
1 minute	94.06±8.43	104.74±11.93	<0.001**
3 minutes	84.43±8.09	99.37±7.08	<0.001**
5 minutes	81.22±9.31	97.41±5.05	<0.001**
10 minutes	82.49±7.30	92.19±4.98	<0.001**

GRAPH 7A



GRAPH 7B

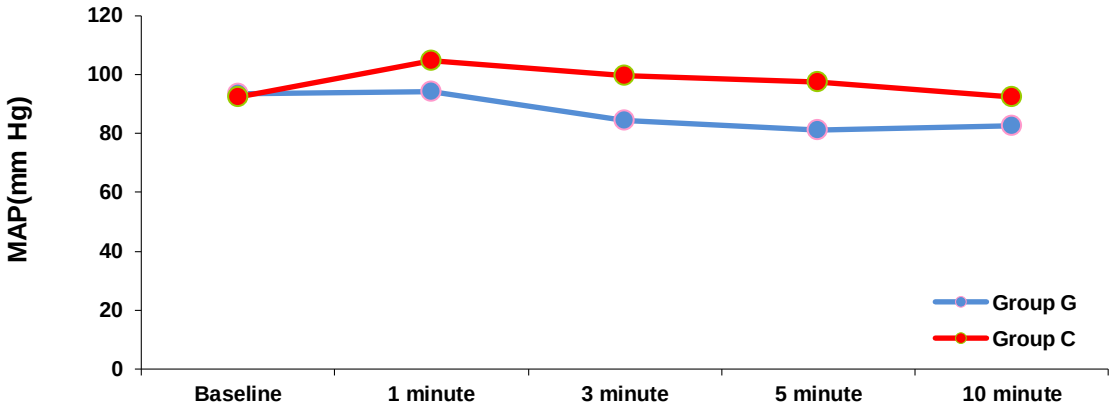


Table 7 and Graph 7a And 7b

COMPARISON OF MEAN ARTERIAL PRESSURE:

GROUP G

The baseline mean and standard deviation of mean arterial pressure in group G was 93.49±7.69. The mean arterial pressures were 94.06±8.43, 84.43±8.09, 81.22±9.31 and 82.49±7.30 at 1 minute, 3 minute, 5 minute and 10 minute time intervals respectively (mean arterial pressure fell below the baseline value).

GROUP C

The baseline mean and standard deviation of mean arterial pressure in group C was 92.26±5.75. The mean arterial pressure were104.74±11.93, 99.37±7.08, 97.41±5.05 and 92.19±4.98 at 1 minute, 3 minute, 5 minute and 10 minute time intervals respectively.

INTERGROUP COMPARISON

The mean blood pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval is clinically lesser in Gabapentin group than in the Clonidine group. At all time intervals P<0.001 indicates it is statistically also highly significant.

The fall to baseline value in the gabapentin group was at 3rd minute and in Clonidine group at 10th minute and statistically it was significant (P<0.01) indicating Gabapentin group showed earlier recovery to baseline values compared to Clonidine group.

Table 8: Sedation score

Sedation score	**Group G**		**Group C**	
	No.	**%**	**No.**	**%**
Score 0	-	-	-	-
Score 1	15	50.0	2	6.66
Score 2	13	43.3	9	30.0
Score 3	2	6.7	19	63.34
Total	30	100.0	30	100.0
Mean ± SD	2.57±0.62		3.73±0.64	

Mean sedation score is significantly less in Group G with P = <0.001**

GRAPH 8

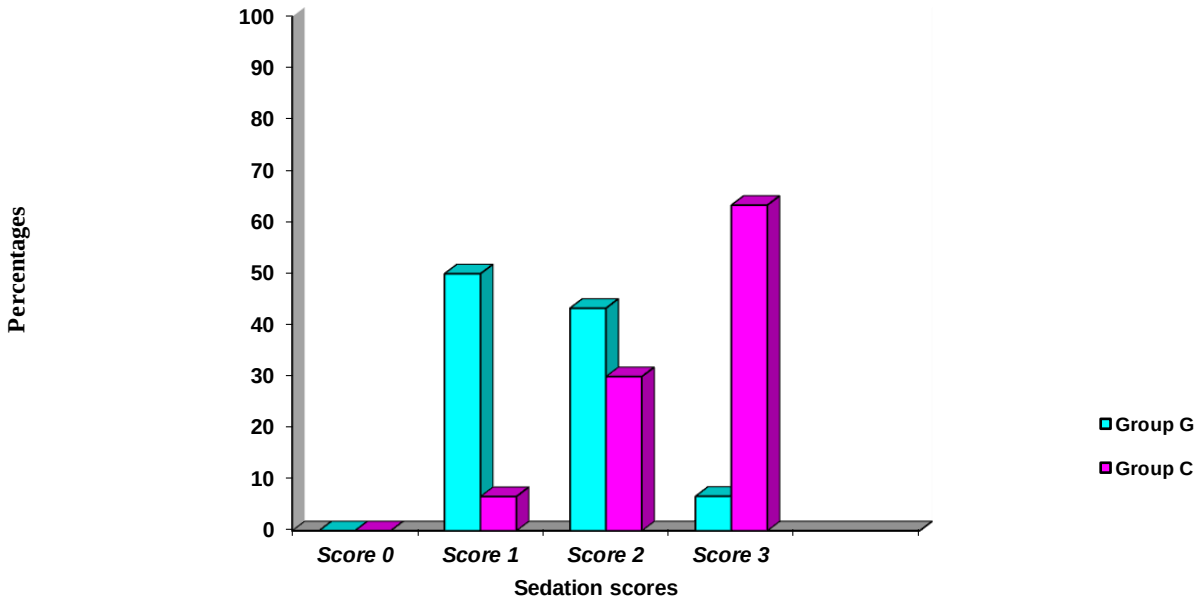


Table 8 and Graph 8

COMPARISON OF SEDATION SCORES:

GROUP G

In Gabapentin group 50%of the patients had a sedation score of 1 followed by 43.3% with sedation score of 2 and rest 6.7% had a score of 3.

GROUP C

In Clonidine group 63.34% of the patients had a sedation score of 3 followed by 30.0% with sedation score of 2 and rest 6.66% had a score of 1.

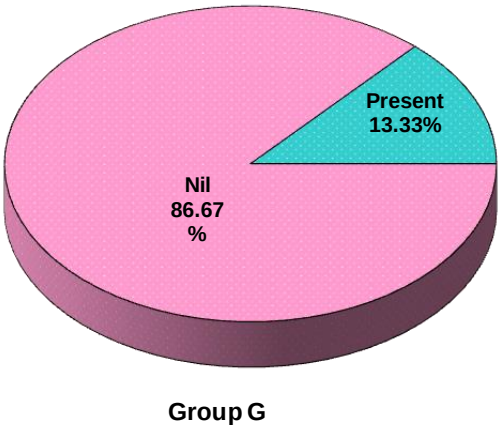
INTERGROUP COMPARISON

The mean sedation scores was found to be clinically and statistically more in Clonidine group than Gabapentin group with p value<0.001.

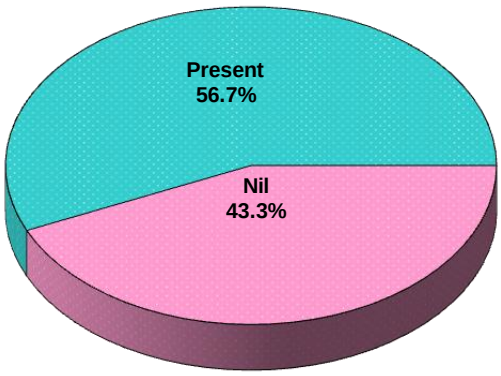
Table 9: Side effects

Side effects	Group G (n=30)		Group C (n=30)	
	No	**%**	**No**	**%**
Nil	26	86.67	13	43.3
Present	4	13.33	17	56.7
Drowsy	2	6.7	15	50.0
dizziness	2	6.6	0	0
Bradycardia	0	0.0	2	6.7
Inference	Incidence of side effects are significantly less in Group G with P<0.001**			

GRAPH 9A



Group G



Group C

GRAPH 9B

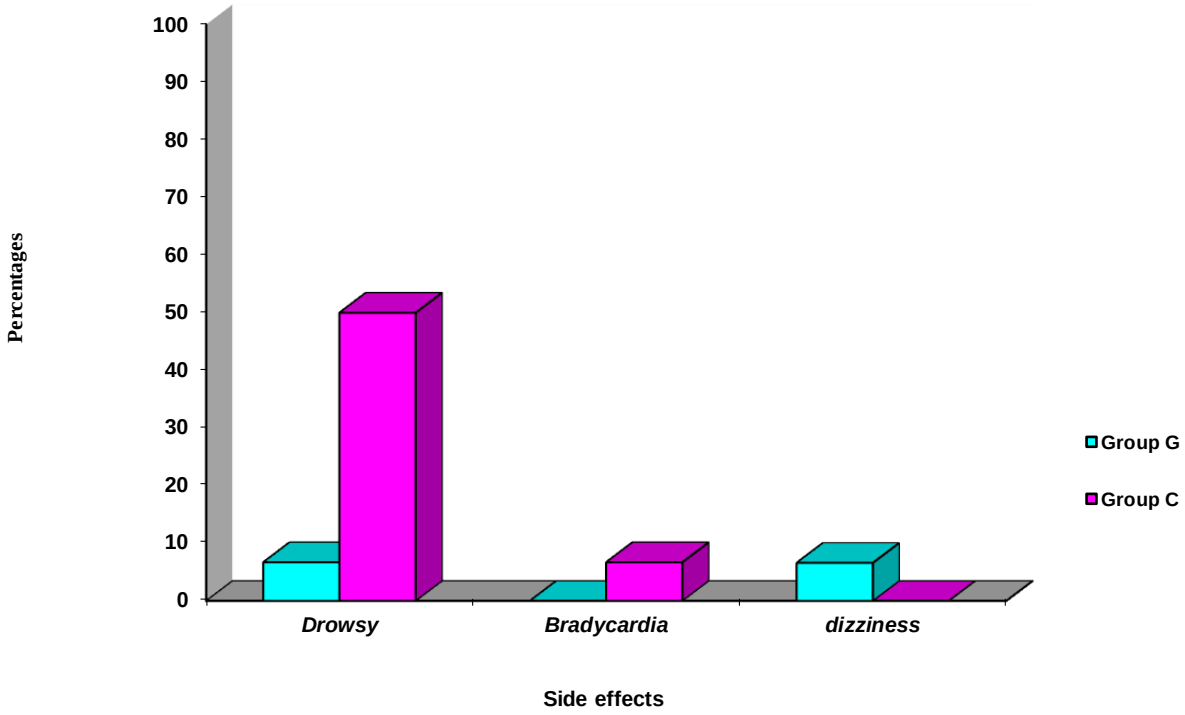


Table 9 and Graph 9A and 9B

COMPARISON OF INCIDENCE OF SIDE EFFECTS:

GROUP G

In Gabapentin group 13.33%of the patients complained of drowsiness(6.7%) and dizziness(6.6%)whereas rest of them did not report any side effects.

GROUP C

In Clonidine group 50.0% of the patients complained of drowsiness whereas 6.7% (2patients) had an episode of bradycardia which was treated by injection Atropine 0.6mg.

INTERGROUP COMPARISON

The incidence of side effects like drowsiness was seen more in Clonidine group than in Gabapentin group , whereas dizziness was seen only in the Gabapentin group.Two patients had an episode of bradycardia in the clonidine group whereas none of the patients in gabapentin group had bradycardia. Overall the Incidence of side effects are significantly less in Group G with P<0.001**

DISCUSSION

Laryngoscopy and endotracheal intubation elicit a reflex cardiovascular response in the form of hypertension and tachycardia in adults. Though well tolerated in healthy adult patients it can have catastrophic consequences in patients with coronary artery disease and cerebrovascular diseases.[1]

There is increased release of catecholamines norepinephrine, epinephrine and vasopressin- the result of which is tachycardia and hypertension. It also causes a rise in intracranial pressure. It is very much essential to minimise the hemodynamic response to laryngoscopy and intubation in high risk patients such as patients with history of coronary artery disease, hypertension and cerebrovascular diseases. To achieve this it is important to understand the dynamic interactions between the drugs used, onset of drug effects and the delicate balance between the therapeutic effects of drugs and the effects of the noxious stimuli. One should avoid over treating these responses which are usually short lived and well tolerated by most patients-*one ounce of prevention is worth a pound of cure*.

Premedication forms an integral part of anaesthetic management and some form of premedication is universally administered before any anaesthesia. The ideal premedicant should be effective and pleasant to be taken orally, have analgesic and non emetic properties, should not impair cardiovascular stability or depress respiration, and should effectively alleviate apprehension of the patient.Several techniques have been proposed to attenuate the hemodynamic responses following laryngoscopy and intubation such as deepening of anesthesia, premedication with drugs like lignocaine, nitroglycerine, βblockers, Calcium channel blockers and opioids.

In our study we have compared clonidine an α_2 adrenergic receptor agonist and an established drug in attenuation of hemodynamic responses to laryngoscopy and intubation with gabapentin which belongs to the class of anticonvulsants and is now being increasingly used not only for neuropathic pain but also for pre and post operative analgesia as well as in control of perioperative stress responses including that of laryngoscopy and intubation.

The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. Although the molecular targets of gabapentin remain unknown, the inhibition of Ca_2^+ flux in muscle cells with a consequent inhibition of smooth muscle contraction might explain the effectiveness of gabapentin in attenuation of the pressor response to laryngoscopy. Thus it may act in a manner similar to Ca_2^+channel blockers.[16]

The attenuating effect of clonidine on hemodynamic responses to airway manipulation has previously been documented by many studies. Dipak L. Raval and other authors[20], Talebi H and colleagues[24], have documented that orally administered clonidine in preanesthetic period attenuates the stress response to laryngoscopy and intubation.

Our reason for studying patients up to 50 years of age was that elderly patients more often take drugs such as antidepressants, hypnotics and antihypertensives. Older patients also exhibit increased sensitivity to drugs and the cardiovascular effects of gabapentin have not been studied extensively. Separate studies are required to study the effect of gabapentin in older age group patients.

We used gabapentin at a single dose of 900mg as Memis and co workers and Fassalouki and co workers have specified doses of 800- 1200mg for attenuation of hemodynamic responses for laryngoscopy and intubation.

Gabapentin s efficacy on attenuating hemodynamic responses following laryngoscopy was revealed by Fassoulaki and colleagues in 2006.[11] In their study they administered gabapentin 1600 mg in four divided doses, at 6 h intervals (starting the day before surgery).They showed SAP and DAP significantly were lower in the gabapentin group than in the control group ($p<0.05$) immediately also in 1, 3, 5 and 10 minute after laryngoscopy but HR did not differ between two groups at any of the times.

Memis and colleagues[13] in their randomised study also studied the effect of gabapentin 400mg versus 800mg on mean arterial pressure and heart rate at induction of anaesthesia and tracheal intubation and compared it with a placebo. Their study showed that patients receiving placebo and 400 mg gabapentin showed a significant increase in blood pressure and heart rate associated with tracheal intubation compared to baseline levels and from patients receiving 800 mg of gabapentin. There was a significant decrease in heart rate and mean arterial pressure in the group receiving 800 mg gabapentin 1, 3, 5 and 10 min after intubation compared to the placebo group and 400 mg gabapentin group.

In our study we used gabapentin in a dose of 900mg 120 minutes prior to surgery. Gabapentin was found to effectively attenuate the rise in SBP, DBP and MAP at 1,3,5 and 10 minutes after intubation. This correlates with the studies done by Fassoulaki and colleagues and also Memis et al. But in our study as we have compared Gabapentin with Clonidine (at a dose of 200micrograms) the differences in heart rate responses was not found to be significant at 1 and 3 minutes. In fact clonidine showed better attenuation of heart rate response at 5 and 10 minutes which was statistically significant. But the increase in heart rate in group gabapentin was not much more than the baseline values indicating that it maintains the heart rate closer to baseline than clonidine group in which the heart rate decreased to less than baseline values.

Seyed Mojtaba Marashi and colleagues[6] in their study found that the highest rates of heart rate, systolic, diastolic and mean arterial blood pressure were in the placebo group in one minute after laryngoscopy, and the lowest rate were in the gabapentin group at the time of 1, 3, 5 and 10 after laryngoscopy, except that the lowest rate of heart rate in 10 min after laryngoscopy was in clonidine group. They also found that clonidine attenuated heart rate at 10 minutes more better than gabapentin, although at 1 and 5minutes they found no significant difference between the clonidine and gabapentin groups.

Our study also correlates with their study in regards to better control of systolic, diastolic and mean arterial pressures in gabapentin group than clonidine group($p<0.001$). We found that clonidine attenuated heart rate response better than gabapentin at both 5 and 10 minutes($p<0.001$) although at 1 and 3 minutes there was no significant difference between the two groups. ($p=0.162$, $p=0.125$). Since we did not have a placebo group so we could not assess the hemodynamic attenuating effects of clonidine and gabapentin in comparison to placebo. The differences in heart rate between their study and ours could have been due to the type of inhalational agent used and its concentration variation.

Kaya and co workers[15] had studied the effect of preoperative gabapentin 800 mg, given 2 h before surgery on intraocular pressure (IOP) and haemodynamic changes in response to endotracheal intubation and concluded that pre treatment with gabapentin 800 mg effectively suppressed the increase in intraocular pressure and attenuated the increase in the MAP but not the HR associated with tracheal intubation.

Kiran S, Verma D[16] in their study compared tab. Gabapentin 800mg and placebo as regards to attenuation of hemodynamic responses following direct laryngoscopy and

tracheal intubation. They showed that SBP, DBP and MAP were significantly low as compared with placebo in patients pretreated with gabapentin but the tachycardiac response was not completely eliminated.

Our study correlates well with these studies regarding control of pressor changes to laryngoscopy and intubation by gabapentin. We also did not find gabapentin to attenuate the heart rate changes to laryngoscopy and intubation better than clonidine at 1 and 3 minutes.($p=0.162$, $p=0.125$).

In yet another study done by Montazeri K and co workers[10] regarding attenuation of the pressor response to direct laryngoscopy and tracheal Intubation: oral clonidine vs. Oral gabapentin premedication showed that compared with clonidine, Gabapentin significantly reduced DBP,SBP, MAP, and RPP changes for 15 min after endotracheal intubation. Compared with placebo, the incidence of HR, SBP, DBP, and MAP percent increase $\geq$ 20% of baseline values were significantly lower in Group Gabapentin but not so with clonidine group when compared to placebo group.

The difference between their study and our study in regards to attenuation of tachycardiac response by gabapentin (which was found to be present in their study) could be as they did not use any inhalational agent for maintenance of anesthesia after laryngoscopy and instead maintained patients on propofol infusion at 150micrograms/kg. This blunting of tachycardia could be attributed to propofol as it is well known that propofol causes decrease in heart rate more than isoflurane (used in our study) which is an inhalational agent.

Previous studies have shown that arterial pressure and heart rate responses are greater when the duration of laryngoscopy exceeds 30 seconds. The previous studies which studied the effect of gabapentin to attenuate the haemodynamic responses to

laryngoscopy and intubation did not comment upon duration of laryngoscopy and intubation. In our study the mean duration of laryngoscopy andintubation did not exceed 15seconds.

The anaesthetic agents also have an important impact on attenuation of the pressor response to laryngoscopy and intubation. In one study propofol and cis-atracurium[11] were used and in another sevoflurane, N_2O and O_2[13] were used. In yet another study propofol and remifentanil were used.[18] We used Thiopentone and succinylcholine(for intubation) followed by vecuronium, and maintained patients on isoflurane(0.6-1%) and nitrous and oxygen(1:1).

In our study at 1and 3 minutes there was no significant differences between the two groups regarding heart rate changes but at 5 and 10 minutes heart rate response to laryngoscopy and intubation in the clonidine group was clinically lesser than gabapentin group and statistically highly significant ($p=0.002$ at 5 minute and $P<0.001$ at 10 minutes). The fall to baseline value in the Gabapentin group was at 5^{th} minute and in Clonidine group at 3^{rd} minute and this indicates Clonidine group showed earlier recovery to baseline values compared to Gabapentin group.

The mean systolic blood pressure, diastolic blood pressure and mean arterial pressure at 1 minute, 3 minute, 5 minute and 10 minute time interval was clinically lesser in Gabapentin group than in the Clonidine group. At 1, 3 and 5 and 10 minutes p value was <0.001, and was statistically highly significant indicating Gabapentin group attenuated the pressor response to laryngoscopy and intubation better compared to group Clonidine .

There are few limitations of this study. Patients with ASA physical status I and II were enrolled in the study, so the results cannot be generalized to the patients with higher

ASA status. The study was conducted in a single centre. A multi-centered larger study may be more informative. Another limitation of our study was that we did not measure the stress mediators, i.e. endogenous plasma catecholamines or cortisol values perioperatively .

The overall various side effects In Gabapentin group was 13.33% out of which drowsiness was in 6.7% and dizziness in 6.6% whereas rest of them did not report any side effects.whereasIn Clonidine group the overall incidence of side effects was 56.7% out of which 50.0% of the patients complained of drowsiness whereas 6.7% (2patients) had an episode of bradycardia which was treated by injection Atropine 0.6mg.

Overall the incidence of side effects are significantly less in Group G with $P<0.001$.

Sedation scores which was measured using four point scale described by Chernik et al showed The mean sedation scores to be clinically and statistically more in Clonidine group than Gabapentin group with p value<0.001.

CONCLUSION

Based on our present comparative study the following conclusions were drawn:

- Oral gabapentin and oral clonidine both help in attenuating hemodynamic responses to laryngoscopy and intubation at doses of 900mg and 200 micrograms respectively.
- Oral gabapentin (900mg) attenuates the increase in systolic blood pressure, diastolic blood pressure and mean arterial pressure associated with laryngoscopy and intubation better than oral clonidine(200micrograms).
- The increase in heart rate response to laryngoscopy and tracheal intubation is not completely eliminated by oral gabapentin although the increase in heart rate is minimal .
- There is no significant difference in changes in heart rate between the two groups of clonidine and gabapentin at 1 and 3 minutes after laryngoscopy and intubation but at the 5^{th} and 10^{th} minute clonidine shows statistically significant lower heart rates than gabapentin. The fall to baseline value in the Gabapentin group was at 5^{th} minute and in Clonidine group at 3^{rd}minute indicating that Clonidine shows earlier recovery to baseline values compared to Gabapentin.
- Incidence of side effects like drowsiness(50%), bradycardia(6.7%) and sedation is more in patients taking oral clonidine compared to patients taking gabapentin. Dizziness(6.7%) was seen only in patients taking gabapentin.
- Hence from our study we can conclude that gabapentin is a better drug compared to clonidine to attenuate the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated.

SUMMARY

Laryngoscopy and intubation causes reflex sympatho-adrenal response in the form of tachycardia and hypertension. This stress response is transient lasting for 5 to 10 minutes and is well tolerated by healthy adult patients. But this stress response can cause catastrophic event in patients with history of hypertension, coronary artery disease, cerebrovascular disease and in elderly patients. Various methods are employed to attenuate this stress response including oral premedication with clonidine and gabapentin.

In the present clinical comparative study we compared oral gabapentin at a dose of 900mg with oral clonidine 200micrograms for attenuating hemodynamic responses to laryngoscopy and tracheal intubation.

Sixty patients of ASA grade 1 and 2 in the age group of 18 years to 50 years, of either sex, posted for elective surgeries under general anaesthesia were selected for the study.Patients were randomly divided on an alternative basis into two groups of 30 each. On the morning of surgery the study medications were given orally with sips of water 2 hour preoperatively .

Group "C" received - 200µg clonidine .

Group "G" received- 900mg gabapentin .

Baseline parameters like pulse rate and systolic blood pressure, diastolic blood pressure, mean blood pressure , oxygen saturation and ECG were recorded, intravenous line were secured and all were given intravenous fluids 5 ml/kg. Temperature and urine output monitoring was done.

The level of sedation was assessed by four point score described by Chernik et al .

Grade 0- patient wide awake.

Grade 1-patient is sleeping comfortably but responding to verbal commands.

Grade 2-deep sleep but arousable.

Grade 3-deep sleep, unarousable.

After 3 mins of pre-oxygenation with 100% oxygen , pre medication was done with 5 micro grams per kg of intravenous glycopyrolate . 2.5micro gram per kg i.v fentanylwas given for analgesia. Patientswere induced with i.vthiopentone 5 mg / kg followed by i.v succinylcholine 2 mg / kg for intubation. Care was taken to note that the time for laryngoscopy was less than 15 seconds in all the patients. Anaesthesia was maintained with N_2O+O_2(1:1)+Isoflurane(0.6-1%). Muscle relaxation wasachieved withi.vvecuronium 0.1mg per kg(loading dose) and 0.02 mg per kg (maintenance dose) later.

The baseline heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was taken as 0 minute value. Thereafter the heart rate , systolic blood pressure , diastolic blood pressure and mean blood pressure were recorded at 1,3,5 and 10 minutes after endotracheal intubation.

Oral gabapentin (900mg) attenuated the increase in systolic blood pressure, diastolic blood pressure and mean arterial pressure associated with laryngoscopy and intubation better than oral clonidine(200micrograms).

The increase in heart rate response to laryngoscopy and tracheal intubation was not completely eliminated by oral gabapentin although the increase in heart rate was minimal . There was no significant difference in changes in heart rate between the two groups of clonidine and gabapentin at 1 and 3 minutes after laryngoscopy and

intubation but at the 5^{th} and 10^{th} minute clonidine showed statistically significant lower heart rates than gabapentin. The fall to baseline value in the Gabapentin group was at 5^{th} minute and in Clonidine group at 3^{rd}minute indicating that Clonidine shows earlier recovery to baseline values compared to Gabapentin.

Incidence of side effects like drowsiness(50%), bradycardia(6.7%) and sedation was seen more in patients taking oral clonidine compared to patients taking gabapentin. The bradycardia was successfully treated by injection atropine 0.6mg.Dizziness(6.7%) was seen only in patients taking gabapentin.

Hence from our clinical comparative study we conclude that gabapentin is a better drug compared to clonidine to attenuate the pressor response associated with laryngoscopy and tracheal intubation, but the tachycardiac response is not completely attenuated.

BIBLIOGRAPHY

1. Henderson J. Airway management in the adult. In: Miller RD, editor. Miller's Anaesthesia, 7 th ed. Churchill Livingstone: Philadelphia; 2010. p. 1573-1610.
2. King BD, Harris LC, Griefenstein FE, Elder JD, Dripps RD. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Br J Anaesth 1951; 12: 556-66.
3. Derbyshire DR, Smith G. Sympatho adrenal responses to anaesthesia and surgery. Br J Anaesth 1984; 56: 725-39.
4. Yokota S, Komatsu T, Yano K, Taki K, Shimada Y.Nagoya.Effect of oral clonidine premedication on hemodynamic response during sedated nasal fiberoptic intubation. J Med Sci. 1998 May;61(1-2):47-52.
5. Backonja M, Beydoun A, Edwards KR. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998; 280:1831–6.
6. Marashi SM, Ghafari MH, Saliminia A: Attenuation of hemodynamic responses following laryngoscopy and tracheal intubation - Comparative assessment of Clonidine and Gabapentin premedication. M.E.J. Anaesth 2009;20 (2):233-237.
7. Shrestha GS, Marhatta MN, Amatya R. Use of Gabapentin, Esmolol or Their Combination to Attenuate Haemodynamic Response to Laryngoscopy and Intubation. Kathmandu Univ Med J 2011;36(4):238-43.
8. Bafna U, Goyal VK, Garg A. A comparison of different doses of gabapentin to attenuate the haemodynamic response to laryngoscopy and tracheal intubation in normotensive patients. J Anaesth Clin Pharmacol 2011;27:43-46.

9. Iftikhar T, Taqi A, Sibtain A, Anjum S, Awan I. Oral gabapentin reduces hemodynamic response to direct laryngoscopy and tracheal intubation. Anaesth Pain & Intensive Care 2011;15(1):17-20.
10. Montazeri K, Kashefi P, Honarmand A, Safavi M, Hirmanpour A. Attenuation of the pressor response to direct laryngoscopy and tracheal Intubation: oral clonidine versus oral gabapentin premedication. Journal of Research in Medical Sciences2011;16:377-86.
11. FassoulakiA,MelemeniA,Paraskeva A, EtropoulosP G:Gabapentin attenuates the pressor changes to direct laryngoscopy and tracheal intubation.Br J Anaesth 2006;96:769-73.
12. Ali AR, El Gohary M, H. Salah El-din A, El-Kerdawy HM, Essa HH. Efficacy of Preoperative Oral Gabapentin in Attenuation of Neuro-Endocrine Response to Laryngoscopy and Endotracheal Intubation. J Med Sci 2009;9:24-9 .
13. Memis D, Turan A, Karamanlioglu B, Seker S, Ture M. Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol 2006; 23:686-90.
14. Kumkum Gupta, Deepak Sharma, and Prashant K. Gupta. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation. Saudi J Anaesth. 2011 Apr-Jun; 5(2): 179–184.
15. Kaya FN, Yavascaoglu B, Baykara M, Altun GT, Gulhan N, Ata F. Effect of oral gabapentin on the intraocular pressure and haemodynamic responses induced by tracheal intubation. ActaAnaesthesiol Scand2008;52:1076-80.
16. Kiran S and Verma D. Evaluation of gabapentin in attenuating pressor response to direct laryngoscopy and tracheal intubation. SAJAA 2008 ; 14(6) : 43-46

17. V.K.F Kong,MGIrwin. Gabapentin : a multimodal peri-operative drug? BJA2007; 99:775-786.
18. Koc S, Memis D, Sut N. The preoperative use of gabapentin, dexamethasone and their combination in varicocele surgery: a randomized controlled trial. AnesthAnalg 2007;105(4):1137-42.
19. S. Sharma , R. Angral , A. Jamwal , K. Bhanotra : Comparative Evaluation Of Gabapentin, Clonidine And Combination Of Both The Drugs To Attenuate The Pressor Response To Direct Laryngoscopy And Intubation.The Internet Journal of Anesthesiology. 2012 Volume 30 Number 4.
20. RavalD , Mehta MK : Oral clonidine for attenuation of pressor response. Indian J. Anaesth. 2002;46 (2) : 124-129.
21. Kumari I, PathaniaVS: A prospective double blind placebo controlled trial of oral gabapentin in attenuation of hemodynamic responses during laryngoscopy and tracheal intubation. J Anaesth Clinical Pharmacology 2009;25(4):439-443.
22. Matot I, Sichel J, Yofe V, Gozal Y: The Effect of clonidine premedication on hemodynamic responses to microlaryngoscopy and rigid bronchoscopy. AnesthAnalg; 2000; 91:828-33.
23. Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesth.2011; 55(1): 26–30.
24. H. Talebi, A. Nourozi, S. Fateh, A. Mohammadzadeh, P. Eghtesadi-Araghi, S. Jabbari and M. Kalantarian, 2010. Effects of Oral Clonidine Premedication on Haemodynamic Response to Laryngoscopy and Tracheal Intubation: A Clinical Trial. Pakistan Journal of Biological Sciences, 13: 1146-1150.

25. Marashi SM, Morabi AA, Ghafari MH, AzimaraghiO,Movafegh A.2012.The Effect of Pre-operative Oral Clonidine or Gabapentin on Post-operative Pain intensity, Morphine Consumption and Post-operative Nausea and Vomiting in Patients Who Undergone Thyroidectomy: A Double-blind Placebo-control Study. J AnesthClin Res 3:206.
26. Prabhakar H, Arora R, Bithal PK, Rath GP, Dash HH. The analgesic effects of preemptive gabapentin in patients undergoing surgery for brachial plexus injury--a preliminary study. J NeurosurgAnesthesiol. 2007 Oct;19(4):235-8.
27. Chandra Kant Pandey et al. Pre-emptive use of Gabapentin significantly decreases post operative& rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaes 2004;51(4):358-363.
28. Kulka, P.J, M. Tryba and M. Zenz. Dose-response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. Anesth Analg1995, 80: 263-268.
29. Laurito CE, Baughman VL, Becker GL.Oral clonidine blunts the hemodynamic responses to brief but not prolonged laryngoscopy. J Clin Anesth1993, 5: 54-57.
30. Richard S. Snell. Snell's clinical anatomy for anaesthesiologists' 5th ed. Philadelphia: Lippincott Williams; 2008;p 64-97.
31. Kayhan Z, Aldemir D, Mutlu H, Ogus E. Which is responsible for hemodynamic response due to laryngoscopy and intubation? Catecholamines, vasopressin or angiotensin. Eur J Anaesth 2005; 22(10): 780-85.
32. Robert K Stoelting. Clonidine In Pharmacology and Physiology in anesthetic practice. Ed by Robert K Stoelting, Simon C Hillier. 4thedn. Lippincott Williams and wilkins. 1999; p 340-345.

33. Hirose H, Maruyama H, Ito K et al. 1993. Glucose-induced insulin secretion and α2-adrenergic receptor subtypes Journal of Laboratory and Clinical Medicine 121: 32-37.

34. Flamez A, De Backer JP, Czerwiec E, Ladure P, Vauquelin G 1997. Pharmacological characterization of I1 and I2 imidazoline receptors in human striatum. Neurochemistry International 30: 25-29.

35. Davies DS, Wing LMH, Reid JL et al. 1997. Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. Clinical Pharmacology and Therapeutics 21: 593-601.

36. Cantor S, et al. 1968. Observations on the hypotensive action of Catapres (ST 155) in man. Medical Journal of Australia 1: 87-91.

37. Lal S, Tolis G, Martin JB, Brown GM, Guyda H 1975. Effect of clonidine on growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone in the serum of normal men. Journal of Clinical Endocrinology and Metabolism 41: 827-832.

38. Warren JB, Dollery CT, Sciberras D, Goldberg MR 1991. Assessment of MK- 467, a peripheral α2-adrenergic receptor antagonist, with intravenous clonidine. Clinical Pharmacology and Therapeutics 50: 71-77.

39. Nilsson-Ehle P, et al. Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. Acta. Med. Scand. 1988; 224: 131-4.

40. Saibene-V,MartinelliG,Vasconi F, Pozza G. Clonidine effect on insulin secretion and lipolysis in man. Acta. Diabetol. Lat. 1978; May-Aug; 15(3-4): 192-7.

41. Robertson, RP and Porte, D Jr: Adrenergic modulation of basal insulin secretion in man. Diabetes 22: 1-8, 1973.

42. Robertson RP, Halter JB and Porte D Jr: A role for alpha-adrenergic receptors in abnormal insulin secretion in diabetes mellitus J. Clin. Invest. 57: 791-95, 1976.

43. Guthrie GP, Miller RE, Kotchen TA, Koerig SH. Clonidine in patients with diabetes and mild hypertension. Clin. Pharmacol. Ther. 1983; 34: 713-7.
44. Satia MC, Shukla ML, Goyal RK. Effect of various antihypertensive drugs on lipid and other biochemical parameters in diabetic and non-diabetic patients. Ind. J. Pharmacol. 1993; 25: 38.
45. Sacerdote AS. Topical clonidine on diabetic gastroparesis. Ann. Intern. Med. 1990; 112: 796.
46. Nicolaon G, Chen AA, Johnston CE et al. 1997. Clonidine decreases vasoconstriction and shivering thresholds, without affecting the sweating threshold. Canadian Journal of Anaesthesia 44: 636-642.
47. Conolly ME, Oates JA, 1977. The clinical pharmacology of antihypertensive drugs II. Clonidine. In: Gross F (ed) Antihypertensive agents. Springerverlag, Berlin p. 583-589.
48. Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. Ann. Pharmacother. 2000; 34: 611-15.
49. Bailey RR, Neale TJ, 1976. Rapid clonidine withdrawal with blood pressure overshoot exaggerated by β-blockade. British Medical Journal, i: 942-943.
50. Briant RH, Reid JL, Dollery CT, 1973. Interaction between clonidine and desipramine in man. British Medical Journal i: 522-533.
51. Pettinger WA, Mitchell HC, Gullner HG 1977. Clonidine and the vasodilating β blocker and antihypertensive drug interaction. Clinical Pharmacology and Therapeutics 22: 164-171.
52. Garrett BN, Kaplan NM 1980. Clonidine in the treatment of hypertension. Journal of Cardiovascular Pharmacology 2 (Suppl. 1): 561-571.

53. Puzantian T, Hart LL. Clonidine in panic disorder. Ann. Pharmacother. 1993; 27: 1351-3.

54. Harmon RJ, Riggs PD. Clonidine for post traumatic stress disorder in preschool children. J. Am. Acad. Child. Adolesc. Psychiatry 1996; 35: 1247-9.

55. Petursson G, Cole R, Hanna C 1984. Treatment of glaucoma using minidrops of clonidine. Archives of ophthalmology 102: 1180-1181.

56. Zubenko GS, Cohen BM, Lipinski JF. 1984. Clonidine in the treatment of mania and mixed bipolar disorder. American Journal of Psychiatry. 141: 1617-1618.

57. Ogbonnaya KI, Arem R. Diabetic diarrhea: Pathophysiology, diagnosis and management. Arch. Intern. Med. 1990; 150: 262-7.

58. Connor DF, et al. A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. J. Am. Acad. Child Adolesc Psychiatry 1999; 38: 1551-9.

59. Pandya KJ, et al. Oral clonidine in post menopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program Study. Ann. Intern. Med., 2000; 132: 788-93.

60. Mikawa K, et al. Oral clonidine premedication reduces vomiting in children after strabismus surgery. Can. J. Anaesth., 1995; 42: 977-81.

61. Oddby-Muhrbeck E. Effect of clonidine on post-operative nausea and vomiting in breast cancer surgery. Anaesthesiology 2002; 96: 1109-14.

62. Lenz T.Clonidine-suppression test revisited. Blood Press, 1998; 7: 153-9.

63. Joris J. Clonidine and ketanserin both are effective treatment for post anaesthetic shivering. Anaesthesiology 1993; 79: 532-9.

64. IP Yam PC. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. Br. J. Anaesth., 1992; 68: 106-8.

65. Gowing L.α2-adrenergic agonists for the management of opioid withdrawal. Available in the Cochrane Library; Issue 1. Chichester: John Wiley: 2004.

66. HoderEL.Clonidine treatment of neonatal narcotic abstinence syndrome. Psychiatry Res., 1984; 13: 243-51.

67. Gourlay SG, et al. Clonidine for smoking cessation. Available in the Cochrane Library; Issue 1. Chichester: John Wiley; 2004.

68. Bonnet F, et al. Post-operative analgesia with extradural clonidine. Br. J. Anesth., 1989; 63: 465-9.

69. Buggy DJ, Mac Dowell C. Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour. Br. J. Anesth., 1996; 76: 319-21.

70. Leckman JF, et al. Clonidine treatment of Gilles de la Tourette's syndrome. Arch. Gen. Psychiatry 1991; 48: 324-8.

71. Roger J Porter, Brian S Meldrum. Anti-seizure drugs: Bertram G Katzung, editor. Basic & clinical pharmacology 2007, USA: McGrawHill companies,Inc,2007: p374-394.

72. Mellick L.B and Mellick G.A. Successful treatment of reflex sympathetic dystrophy with gabapentin.Am.J.Emerg.Med.1995;13:96-96.

73. Field MJ, Oles RJ, Lewis AS, McCleary S, Hughes J, Singh L. Gabapentin (neurontin) and S-(þ)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br JPharmacol 1997a; 121:1513–22.

74. RowbothamMC.Treatment of neuropathic pain: perspectives on current options. In Pain -An Update Review: Refresher Course Syllabus. IASP 2005; p107-19.

75. LuoZD.Upregulation of dorsal root ganglion $\alpha_2\delta$ calcium channel subunit and its correlation with allodynia in spinal nerve injured rats. J Neurosci 2001;21:1868–75.

76. Taylor CP, Gee NS, Su TZ, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res. 1998; 29:233–249.

77. Bertrand.S.G, M.G. Purisai, S.E. Wolfe.2001. The anticonvulsant, antihyperalgesic agent gabapentin is an agonist at brain gamma-amino butyric acid type B receptors negatively coupled to voltage-dependent calcium channels. J. Pharmacol. Exp. Ther., 298: 15-24.

78. Gee NS, Brown JP, Dissanayake VU,. The novel anticonvulsant drug,gabapentin (neurontin), binds to the a2d subunits of calcium channel. J Biol Chem. 1996; 271:5768–5776.

79. Fink.K, D.J. Dooley, W.P. Meder, N. Suman-Chauhan, S. Duffy, H. Clusmann and M. Göthert, 2002. Inhibition of neuronal Ca2+ influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology, 42: 229-236.

80. Maneuf, Y.P., M.I. Gonzalez, K.S. Sutton, F.Z. Chung, R.D. Pinnock and K. Lee, 2003. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol. Life Sci., 60: 742-750.

81. Sarantopoulos, C., B. McCallum, W.M. Kwok and Q. Hogan, 2002. Gabapentin decreases membrane calcium currents in injured as well as control mammalian primary afferent neurons. Reg. Anaesth. Pain Med., 27: 47-57

82. Cai, K., R. P. Nanga, et al.The Impact of Gabapentin Administration on Brain gaba andglutamateconcentrations:A7T(1)hmrsstudy.Neuropsychopharmacology,2012;67:125-28 .

83. Elwes RDB, Binnie CD — Clinical pharmacokinetics of newer antiepileptic drugs. Lamotrigine, vigabatrin, gabapentin and oxcarbazepine. ClinPharmacokinet, 1996;30:403-415.

84. Beydoun A, Uthman BM, Sackellares JC. Gabapentin: pharmacokinetics, efficacy, and safety. ClinNeuropharmacol 1995;18:469–81.

85. Comstock TI, Sica DA, Bockbrader HN et al. — Gabapentin pharmacokinetics in subjects with various degrees of renal function. J ClinPharmacol, 1990;30:862.

86. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. Drugs. 1993;46:409–427.

87. Gidal B, Billington R — New and emerging treatment options for neuropathic pain. Am J Manag Care, 2006; 12:269-278.

88. Kakimoto, S., T. Ozawa, et al.2012.Pharmacological and clinical profile of gabapentin enacarbil: a novel drug for the treatment of restless legs syndrome. Nihon YakurigakuZasshi140(2): 85-92.

89. Nicholson B. Gabapentin use in neuropathic pain syndrome. ActaNeurolScand 2000;116:359–71.

90. Mohammadi SS, Seyedi M. The Effects of gabapentin on early postoperative pain, nausea and vomiting in laparoscopic surgery for assisted reproductive technologies.Pak J Biol Sci. 2008 Jul 15;11(14):1878-80.

91. Clivatti J, Sakata RK, Issy AM. Review of the use of gabapentin in the control of postoperative pain.Rev Bras Anestesiol. 2009 Jan-Feb;59(1):92-8, 87-92.

92. Dauri M et al. Gabapentin and pregabalin for the acute post-operative pain management. A systematic-narrative review of the recent clinical evidences.Curr Drug Targets. 2009 Aug;10(8):716-33

93. Dahl JB,MathisenO,Monichie S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain.ActaAnaesthesiol Scand. 2004 Oct;48(9):1130-6.

94. Turan A et.al. The analgesic effects of gabapentin after total abdominal hysterectomy.AnesthAnalg. 2004 May;98(5):1370-3.

95. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, Singh U, Singh PK. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J NeurosurgAnesthesiol. 2005 Apr;17(2):65-8

96. Madhuri S Kurdi, SafiyaShaikh, AshwiniHalesh "Gabapentin –A Novel Analgesic" Karnataka Anaesthesia Journal 2009 Oct 10(2):1-3.

97. Guttuso Jr. Th, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet 2003;361:1703–5.

98. Leung, J.M., L.P. Sands, M. Rico, K.L. Petersen and M.C. Rowbotham et al., 2006. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology, 67: 1251-1253.

99. Omran AF, Mohamed AER. A randomized study of the effects of gabapentin versus placebo on post-thoracotomy pain and pulmonary function. Eg J Anaesth2005;21:277-81.

100. Nikolajsen, L., N.B. Finnerup, S. Kramp, A.S. Vimturp, J. Keller and T.S. Jensen, 2006. A randomized study of the effects of gabapentin on post amputation pain. Anaesthesiology, 105: 1008-1015.

101. Hachad, Houda; Ragueneau-Majlessi, Isabelle; Levy, Rene H.New Antiepileptic Drugs: Review on Drug Interactions. Therapeutic Drug Monitoring:February 2002;24(1)91-103.

102. Sivenius J., Kalviainen R., Ylinen A., Riekkinen P.. Double-blind study of gabapentin in the treatment of partial seizures.Epilepsia 1991; 32: 539-542.

103. Turck D, Vollmer KO, Bockbrader H, Sedman A. Dose-linearity of the new anticonvulsant gabapentin after multiple oral doses.Eur J ClinPharmacol 1989; 36(Suppl): A310.

ANNEXURE I - PROFORMA

A COMPARATIVE STUDY OF CLONIDINE AND GABAPENTIN FOR ATTENUATING HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION

INVESTIGATOR-Dr.Ananya**GUIDE-**Dr.Dinesh.K

NAME: AGE: SEX: WT:HOSPITAL NO. :
DEPT: ASA GRADING: DIAGNOSIS AND OP :

PROTOCOL:premed -At 10:00pm- Rantac 150 mg + diazepam-10mg. At 7:30 am-Tab Rantac-150mg

2 hrs before surgery -Tab. Clonidine- 200microgram / Tab. Gabapentin-900mg

PREANAESTHETIC EVALUATION-

GENERAL PHYSICAL EXAMINATION:

PALLOR : CLUBBING: ICTERUS: OEDEMA:

LYMPHADENOPATHY: BP: PR: RR:

SYSTEMIC EXAMINATION- CVS: RS:

INVESTIGATIONS

URINE MICROSCOPY- Hb%- BT/CT - BLOOD UREA- CREATININE- RBS- Na+ K+ URINE SUGAR- ALBUMIN-

	PRE INDUCTION	POST INDUCTION			
		1 MIN	3 MIN	5 MIN	10 MIN
HEART RATE					
SYSTOLIC BP					
DIASTOLIC BP					
MAP					

SEDATION SCORING- grade 0- patient wide awake SIDE EFFECTS-

grade 1- patient sleeping but responds to commands
grade 2-deep sleep but arousable
grade 3- deep sleep, unarousable

ANNEXURE II - KEYS TO MASTER CHART

Ip.No. : Inpatient Number

DBP : Diastolic Blood Pressure

ENT : Ear Nose Throat

FESS : Functional endoscopic sinus surgery

SBP : : Systolic Blood Pressure

M : male

F : Female

ASA : American Society of Anaesthesiologist Grade

DUB : Dysfunctional Uterine Bleeding

LAVH : Laparoscopic Assisted Vaginal Hysterectomy

Lap. : Laparoscopic

MAP : Mean Arterial Pressure

MLS : Micro Laryngeal Surgery

MRM : Modified Radical Mastectomy

LTO : Laparoscopic Tubal Occlusion

PROFORMA

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PREANAESTHETIC EVALUATION-

GENERAL PHYSICAL EXAMINATION:

PALLOR : CLUBBING: ICTERUS: OEDEMA:

LYMPHADENOPATHY: BP: PR: RR:

SYSTEMIC EXAMINATION- CVS: RS:

INVESTIGATIONS

URINE MICROSCOPY- Hb%- BT/CT - BLOOD UREA- CREATININE- RBS- Na+ K+ URINE SUGAR- ALBUMIN-

	PRE INDUCTION	POST INDUCTION			
		1 MIN	3 MIN	5 MIN	10 MIN
HEART RATE					
SYSTOLIC BP					
DIASTOLIC BP					
MAP					

SEDATION SCORING- grade 0- patient wide awake SIDE EFFECTS
grade 1- patient sleeping but responds to commands
grade 2-deep sleep but arousable
grade 3- deep sleep, unarousable

CLONIDINE

SL. NO.	NAME	AGE	SEX	IP.NO	Wt.	SURGERY	BASELINE				FROM ONSET OF LARYNGOSCOPY															
											1 MIN				3 MIN				5 MIN				10 MIN			
							HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP
1	FARHANA	20	F	685500	50	TONSILLECTOMY	72	104	70	81.333	78	110	78	88.67	84	110	76	87.333	76	108	80	89.333	69	108	78	88
2	JAYAMMA	28	F	693149	45	LAP.APPENDICECTOMY	74	126	84	98	79	134	98	110	74	130	85	100	68	128	86	100	65	130	88	102
3	RAMAVATHI	43	F	687492	65	LAVH	74	119	75	89.667	95	124	89	100.7	94	120	76	90.667	80	119	82	94.333	76	118	82	94
4	AYESHA FIRDOS	20	F	692040	55	LAP.TUBECTOMY	90	105	76	85.667	95	122	75	90.67	114	116	82	93.333	96	116	80	92	88	120	80	93.333
5	TABASUM KOUSAR	38	F	691486	90	LAVH	80	120	77	91.333	90	130	84	99.33	94	128	86	100	90	127	86	99.667	82	128	84	98.667
6	ASHWATHAMMA	35	F	691457	50	TOTAL THYROIECTOMY	102	136	90	105.33	90	136	96	109.3	94	138	98	111.33	92	140	94	109.33	90	136	94	108
7	SHAILA	36	F	699896	65	FIBROADENOMA L BREAST	80	110	80	90	95	118	78	91.33	88	116	76	89.333	82	110	78	88.667	78	112	76	88
8	NAGARATHNAMMA	48	F	730294	55	PAN ENDOSCOPY	82	120	79	92.667	89	128	86	100	86	128	84	98.667	86	122	86	98	80	121	88	99
9	MANISH KUMAR	21	M	671660	85	TONSILLECTOMY	90	136	80	98.667	94	142	84	103.3	90	134	86	102	82	134	84	100.67	82	130	85	100
10	SALEEM	28	M	720856	60	MLS	73	119	74	89	90	123	80	94.33	84	120	82	94.667	80	118	82	94	82	120	78	92
11	RAMAKRISHNA	48	M	720769	60	CHOLECYSTECTOMY	56	112	72	85.333	66	143	94	110.3	64	140	83	102	66	138	80	99.333	60	134	84	100.67
12	MANJULAMMA	27	F	735635	50	CHOLECYSTECTOMY	78	110	74	86	62	120	80	93.33	60	126	82	96.667	57	127	79	95	50	128	80	96
13	BYRAMMA	45	F	735416	67	LAP CHOLECYSTECTOMY	61	119	74	89	64	119	89	99	65	123	88	99.667	64	130	84	99.333	60	132	85	100.67
14	NAGAMANI	32	F	718770	57	EXCISION	56	130	70	90	107	138	78	98	97	128	83	98	90	119	87	97.667	90	123	96	105
15	RATHNAMMA	46	F	711716	53	TOTAL THYROIDECTOMY	69	103	79	87	92	163	118	133	88	123	81	95	75	101	80	87	66	115	81	92.333
16	SUBRAMANYAM	27	M	638758	66	SEPTAL REPAIR	105	119	81	93.667	108	128	86	100	99	133	97	109	84	135	86	102.33	80	126	93	104
17	BHARATHI	44	F	721536	60	FESS	112	122	77	92	115	156	128	137.3	110	130	80	96.667	102	138	85	102.67	94	139	88	105
18	HANUMAKKA	35	F	717463	51	RT. HEMITHYROIDECTOMY	78	100	64	76	97	132	93	106	84	120	86	97.333	81	117	86	96.333	86	118	92	100.67
19	RATHNAMMA	38	F	743146	63	WERTHEIM S HYSTERECTOMY	73	101	74	83	79	110	77	88	101	108	77	87.333	65	124	83	96.667	70	128	81	96.667
20	SOLOMON	47	M	735148	78	BIOPSY	74	103	74	83.667	81	139	97	111	78	126	94	104.67	78	126	90	102	72	120	86	97.333
21	SHARADAMMA	30	F	643950	50	TOTAL THYROIDECTOMY	86	130	80	96.667	98	158	87	110.7	99	154	86	108.67	51	140	84	102.67	70	132	81	98
22	BHARATHI	29	F	742613	54	TOTAL THYROIDECTOMY	83	124	70	88	88	148	117	127.3	85	124	75	91.333	88	124	75	91.333	83	120	81	94
23	PAPPAKKA	45	M	688417	60	WEDGE BIOPSY	81	99	74	82.333	105	133	91	105	75	130	90	103.33	75	124	86	98.667	76	124	82	96
24	MALLIKA	20	F	747126	50	LAP. APPENDICECTOMY	78	114	72	86	98	135	85	101.7	102	138	85	102.67	86	126	86	99.333	72	120	80	93.333
25	SUMITHRA	21	F	742802	55	EXCISION	88	132	80	97.333	110	150	88	108.7	112	152	90	110.67	85	130	82	98	83	130	80	96.667
26	VANAJA	35	F	767322	65	LAP. APPENDICECTOMY	84	136	82	100	112	154	90	111.3	108	150	88	108.67	92	135	83	100.33	78	130	79	96
27	PREMA	27	F	767037	65	LAP. APPENDICECTOMY	80	140	83	102	102	146	90	108.7	106	142	88	106	94	140	80	100	80	138	82	100.67
28	SRINATH	34	M	771301	76	DISCETOMY	86	118	68	84.667	95	125	75	91.67	96	124	70	88	90	120	72	88	82	122	72	88.667
29	DIWAKAR	30	M	774926	77	DECOMPRESSION	84	134	76	95.333	106	150	82	104.7	105	148	80	102.67	92	135	82	99.667	70	130	80	96.667
30	MUNIYAPPA	49	M	765000	56	FEEDING JEJUNOSTOMY	72	138	78	98	97	155	86	109	98	148	84	105.33	90	140	80	100	70	132	80	97.333