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ORIGINAL ARTICLE

ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION USING INTRA-ORAL IVABRADINE: A CLINICAL STUDY

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ABSTRACT: BACKGROUND AND OBJECTIVES: Rapid and dramatic hemodynamic changes which adversely affect the patient may occur during laryngoscopy and intubation. The present study evaluates the effect of oral ivabradine on the hemodynamics during laryngoscopy and endotracheal intubation in patients undergoing surgical procedures under general anesthesia. **METHODS:** A prospective randomized, single blinded study was conducted in 50 ASA- I adult patients undergoing various procedures under general anesthesia. The patients were randomly divided into two groups. Patients in group I (test group) (n=25) received oral Ivabradine, 5mg one tab at 6.00pm on the evening before the day of surgery and one 5mg tab one hour before intubation. Patients in group II (control group) (n=25) received placebo. Hemodynamic variables were recorded from pre-operative period to 10 minutes after intubation. **RESULTS**: There was not a very significant increase in the hemodynamic parameters in response to laryngoscopy and intubation in the Test group, when compared to the control group and the minimal raise also returned to baseline immediately within a minute. **INTERPRETATIONS AND CONCLUSION**: Ivabradine is an extremely useful drug to prevent abnormal increase in heart rate and minimizes the extent of hypertension seen during laryngoscopy and endotracheal intubation.

KEYWORDS: Ivabradine, attenuation, hemodynamic responses, laryngoscopy, intubation.

INTRODUCTION: Endotracheal intubation is one of the most commonly performed procedures, where the role of the anesthesiologists in patient care is noteworthy.

Rapid and dramatic hemodynamic changes which adversely affect the patient may occur during the peri-operative period.[1] Hypertension and tachycardia have been recognized since 1950's as commonly associated with intubation under light anaesthesia. This is usually most evident during laryngoscopy and manipulation of epiglottis.

These changes are probably of little consequence in healthy patients. However failure to blunt the response to intubation may have disastrous consequences in patients with hypertension, raised intracranial pressure, aneurysmal vascular disease, and diseased cerebral vasculature or with ischaemic heart disease.[2]

Complications that might arise because of cardiovascular responses to laryngoscopy and intubation are acute left ventricular failure, arrhythmias, intracranial haemorrhage and pulmonary oedema. Convulsions may be precipitated in eclamptic patients. Almost all types of dysrhythmias have been reported in addition to sinus tachycardia and sinus bradycardia.

Various strategies have been applied to attenuate these responses in high risk individuals.[3]

These include topical and intravenous lignocaine, deep inhalational anaesthesia, ganglion

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blockers, precurarization, narcotics (Morphine, Buprenorphine, Fentanyl and Alfentanyl), adrenoceptor blocking drugs, vasodilators, Nitroglycerine and Calcium channel blockers and manipulations like minimizing the duration of laryngoscopy to less than 15 seconds and placement of supraglottic devices like laryngeal mask airway (LMA) etc.

WHY IVABRADINE, WHY NOT A BETA BLOCKER? Ivabradine is a very unique drug in medical literature. Classified as a cardiotonic agent, Ivabradine is a highly selective inhibitor of 'I_f' channels (Funny current or funny channels or pacemaker current). 'If' blockade results in a decrease in the slope of spontaneous depolarisation, leading to an increase in the time interval between successive action potentials in the SA node, thus decreasing the heart rate.

Ivabradine binds to the intracellular aspect of the 'I_f' channel and inhibits it in a dose and voltage dependent manner. As the binding site is located intracellularly, ivabradine requires an open 'If' channel to reach to its binding site.[22]

It is quite different from a beta blocker. Ivabradine reduces the heart rate without jeopardizing hemodynamics in unhealthy, compromised patients.[4] The drug can be used not only in hypertensive patients but also in normotensive patients.

It has no significant negative inotropic effect like a Beta-blocker and can be even used in patients with bronchial asthma where beta blockers are contra-indicated.

It doesn't alter the metabolism in diabetic patients and doesn't blunt the hypoglycemic responses and does not increase the sensitivity of diabetic patients to oral hypoglycemic agents. In this aspect ivabradine scores significantly over a beta-blocker in all compromised patients.[5]

Ivabradine reduces the heart rate without producing a precipitous fall in blood pressure; hence it is useful in patients with angina pectoris, coronary artery disease (CAD), cardiac failure, obstructive cardiomyopathies and in all conditions where the myocardial oxygen supply is endangered and myocardial oxygen demand is increased.[6, 7]

By not allowing the heart rate to increase, Ivabradine conserves the oxygen reserves of the myocardium and reduces the myocardium oxygen demand.[8] Hence in every aspect Ivabradine is an ideal drug to be used during general anesthesia procedures in view of its multiple benefits on the myocardium.

The present study evaluates the effect of oral ivabradine on the hemodynamics during laryngoscopy and endotracheal intubation and also during the operative procedure in patients undergoing surgical procedures under general anesthesia.

MATERIALS AND METHODS: The study was conducted in fifty adult patients undergoing various procedures under general anesthesia, belonging to ASA Grade- 1 physical status, after informed consent. The patients in the age group of 15-45 years comprising both sexes were included in the study.

Patients underwent ENT and HEAD and NECK procedures like Functional Endoscopic Sinus Surgery, Modified Radical Mastoidectomy, Total thyroidectomy, Hemithyroidectomy, Tonsillectomy, Deviated nasal septum etc.

All the patients were assessed clinically preoperatively and presence of any medical disorder and history of drug intake was ruled out. Patients with H/O chest pain/palpitations/syncope, H/O Respiratory problems, and Hepatic or Renal problems were excluded from the study.

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Patients with the base line heart rate<60 beats per minute, base line systolic blood pressure <100mm Hg and those with ECG abnormalities were excluded from the study.

Patients in whom intubation was thought to be difficult were also excluded from the study. All the patients underwent the following investigations, namely complete urine analysis, haemogram, blood chemistry, x-ray chest and a pre-operative ECG.

The patients were randomly allocated in to two Groups, Test and Control (having 25 patients in each group).

GROUP-1-TEST GROUP: Comprising of 25 patients, who received oral Ivabradine, 5mg one tab at 6.00pm on the evening before the day the surgery and one 5mg tab one hour before intubation.

GROUP-2-CONTROL GROUP: Comprising 25 patients, who received placebo.

The premedication, induction agent and muscle relaxant to facilitate intubation were standardized for both the groups.

Intravenous cannulation was done with 18G cannula after shifting the patient into the waiting area of the operation theatre, and connected to a drip of ringer lactate solution. Premedication with Glycopyrrolate 0.2mg i.m and Ondansetron 4mg were given slowly intravenously, 20 minutes before induction. Patient was connected to non- invasive blood pressure monitors, pulse oximeter probe and electrocardiographic leads (limb lead-2). All patients were pre oxygenated with 100% oxygen for 3 minutes.

The patient was induced by Thiopentone sodium (5mg/kg body weight). Intubation was facilitated by using Succinylcholine 1.5mg/kg i.v. The lungs were ventilated with 100% oxygen for 60 seconds. Intubation was timed at 60 minutes after ivabradine pre-treatment in group-1 and 60 min after placebo in group -2 (correlating with peak action of the drug). Intubation was achieved with an appropriate size oral cuffed, portex endotracheal tube by the aid of Macintosh laryngoscope blade.

The time taken for intubation did not exceed 20 seconds (intubation that needed more than 20 seconds was excluded from the study). Anaesthesia was maintained with Vecuronium bromide 0.08mg/kg top-up doses; and intermittent positive pressure ventilation with nitrous oxide and oxygen in the ratio of 66%: 33% using circle absorber system connected to the Boyle's machine.

Surgery was not allowed to commence till the recordings were completed which was around ten minutes. At the end of the surgery, neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and glycopyrrolate (0.04mg/kg). All the patients were followed in the post-operative period. Any incidence of adverse effects of Ivabradine was looked for in the post-operative period in the comparing two groups.

The parameters recorded were:

1. Heart Rate.
2. Systolic Blood Pressure.
3. Diastolic Blood Pressure.
4. Mean Arterial Pressure.

Ten minutes after the intubation, after taking the recordings of hemodynamic parameters, fentanyl 2mcg/kg and inhalational agent sevoflurane were introduced into the anaesthesia technique along with N2O+ O2 + vecuronium by the closed circuit with circle absorber.

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The recordings were noted at various intervals as detailed below, from the study conducted:

1. Pre-operatively i.e. after premedication (basal line value).
2. At induction/intubation.
3. 1 minute after intubation.
4. 3 minutes after intubation.
5. 5 minutes after intubation.
6. 8 minutes after intubation.
7. 10 minutes after intubation.

Tests of Significance between groups were carried out by Student t-test or modified t-test.

RESULTS: Fifty patients, undergoing elective non-cardiac surgery were selected for the study. The patients were randomly divided into two groups of 25 patients each.

Group-I- Test Group- Patients who received Ivabradine pre-treatment.

Group-II- Control Group- Patients who received placebo.

The Test Group comprises of 10 males and 15 females, and the Control Group comprises of 17 males and 8 female patients. The range for ages was 15-45 in both the study groups. The range for weight was 38-52 kg in both the study groups. There was no statistically significant difference ($p>0.05$).

TIME INTERVAL	GRP	PR	SBP	DBP	MAP
PRE-OP	**T**	80.22	121.56	77.61	92.3
	C	104.56	129.76	82.64	98.35
	P VALUE	0.000	0.001	0.016	0.002
DURING INTUBATION	**T**	84.72	127.22	81.39	96.67
	C	119.92	140.48	92.4	108.43
	P VALUE	0.000	0.000	0.000	0.000
AT 1 min	**T**	78.52	125.16	77.44	93.35
	C	117.32	140.04	89.88	106.6
	P VALUE	0.000	0.000	0.000	0.000
AT 3 min	**T**	74.36	123.16	74.48	90.71
	C	113.36	132.76	87.2	102.39
	P VALUE	0.000	0.000	0.000	0.000
AT 5 min	**T**	73.44	123.24	76.4	92.01
	C	112.04	133	86.96	102.31
	P VALUE	0.000	0.000	0.000	0.000
AT 8 min	**T**	73.16	122	74.52	90.31
	C	111.24	133	83.68	99.96
	P VALUE	0.000	0.000	0.000	0.000
AT 10 min	**T**	73.20	120.16	74.80	89.92
	C	110.84	134	87.32	102.88
	P VALUE	0.000	0.000	0.000	0.000

SUMMARY OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPYAND INTUBATION

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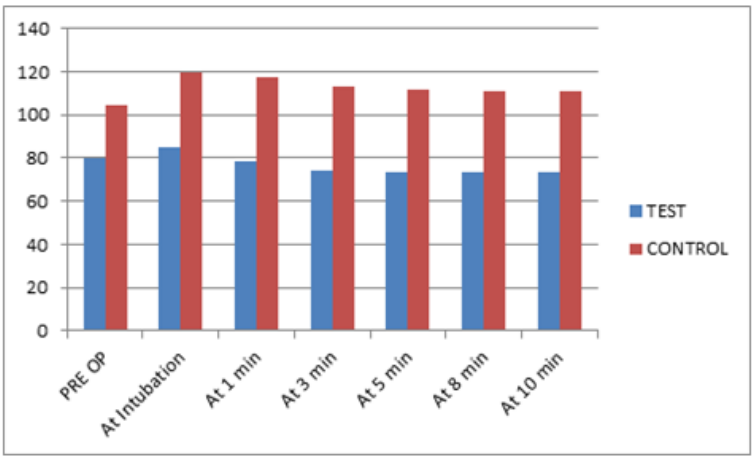
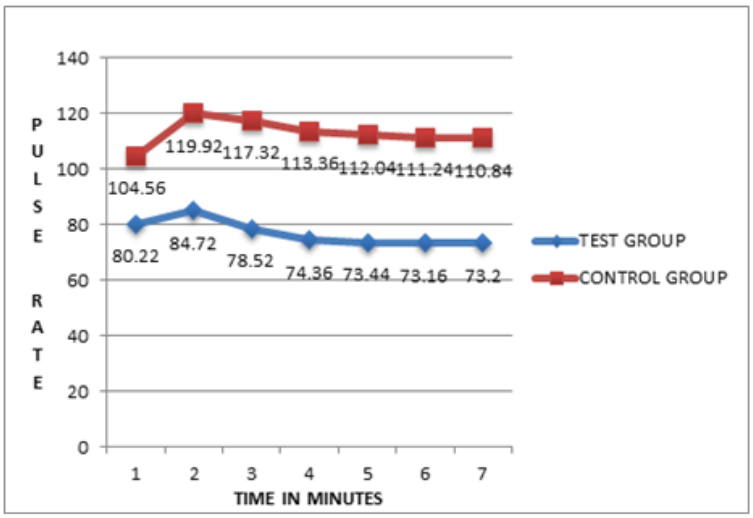
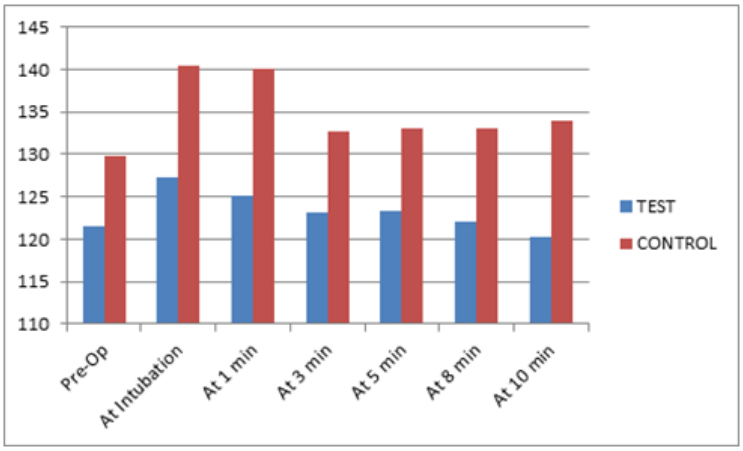
T-TEST; C-CONTROL





PULSE RATE VARIATIONS



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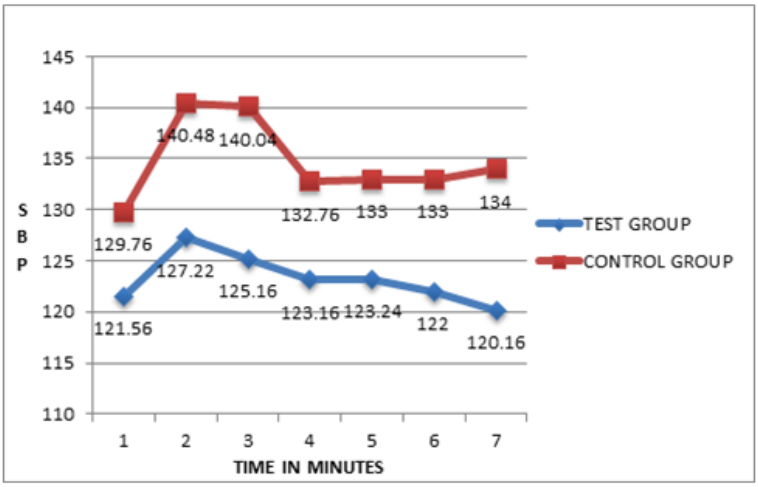
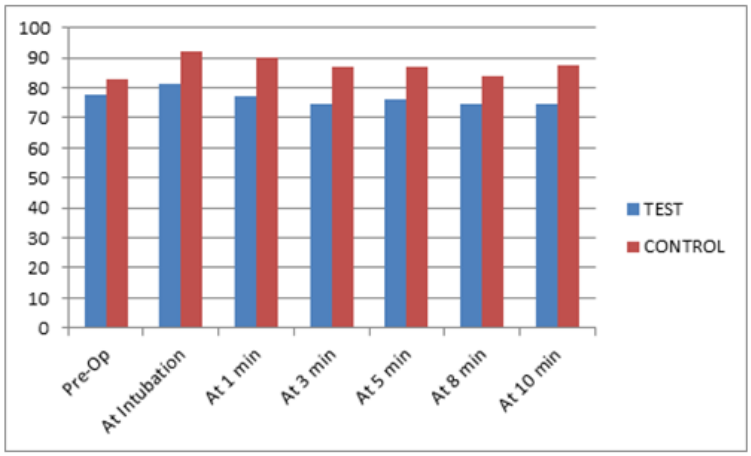
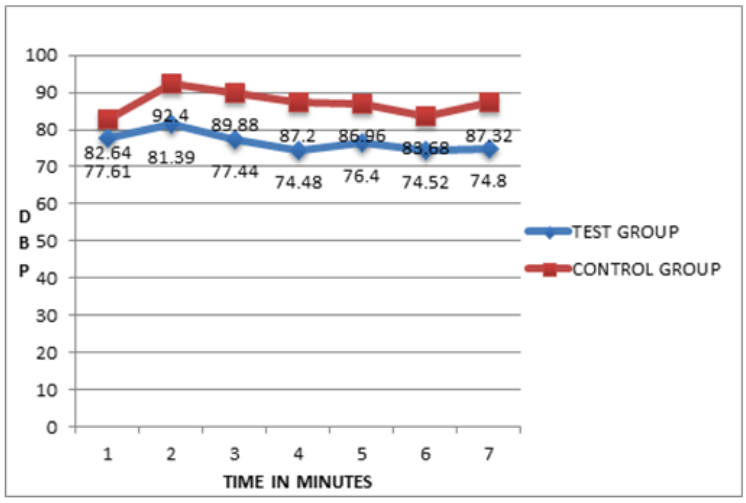


SYSTOLIC BLOOD PRESSURE VARIATIONS





DIASTOLIC BLOOD PRESSURE VARIATIONS

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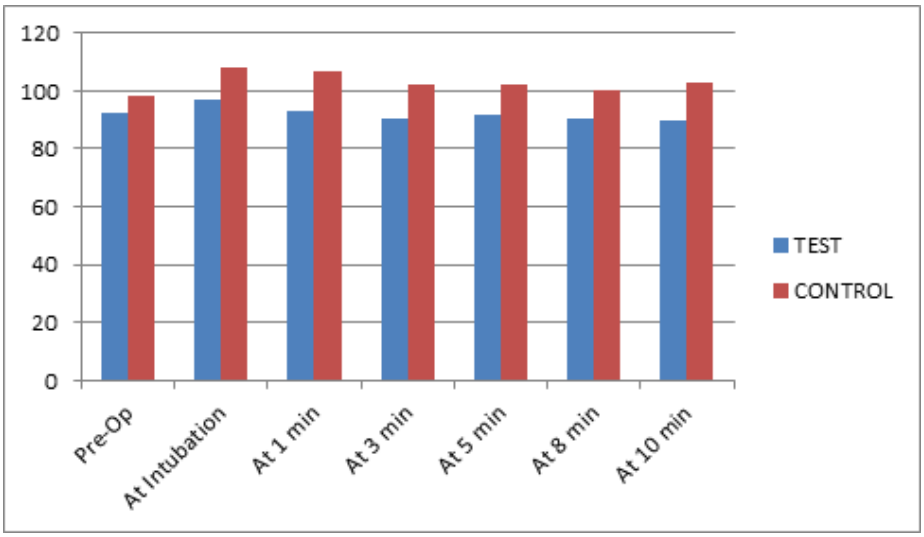

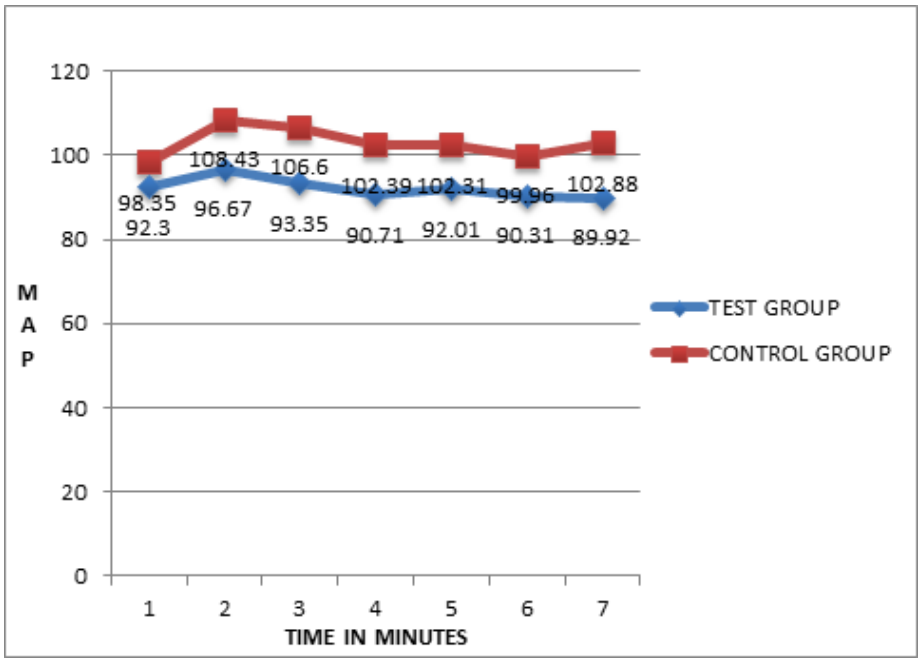

MEAN ARTERIAL PRESSURE VARIATIONS

The difference in the hemodynamic parameters recorded preoperatively, during intubation and at 1, 3, 5, 8 and 10 minutes between the two groups was found to be statistically significant (p value < 0.05).

DISCUSSION: Cardiac and hemodynamic disturbances following Laryngoscopy and endotracheal intubation with traditionally used anesthetic techniques were first reported by REID and BRACE in 1940.[9] These reflex cardiovascular effects in anaesthetized patients include rise in arterial pressures (SBP, DBP, MAP) and heart rate, and they peak approximately 30-45 seconds after laryngoscopy.

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These changes which are transient may lead to serious and life threatening complications in patients with cardiovascular and cerebral diseases.

Various methods to attenuate the sympathetic response to laryngoscopy have been studied, such as topical anesthesia of the pharynx along with superior laryngeal block, intratracheal lidocaine spray, intravenous lidocaine, deeper planes of inhalational anesthesia, beta blockers, alpha blockers, combined alpha-beta blockers like Labetalol, sodium nitroprusside, nifidepine, nitroglycerine (intranasal, intraoral, intravenous), narcotics such as morphine, fentanyl etc.[10-13]

In the present study, oral Ivabradine, was used to attenuate the haemodynamic responses to laryngoscopy and endotracheal intubation and the same were compared with a placebo group.

Blood pressure and heart rate response to laryngoscopy and intubation was studied in both the groups who received the same drugs for induction and intubation.

The pre-induction parameters of Haemodynamics (i.e. after premedication) showed a slight increase in the systolic, diastolic and mean arterial pressures, when compared to the values noted at the pre anaesthestic evaluation. The difference was not statistically significant, and these values were taken as basal values.

After induction and intubation the surgeon was not allowed to operate till ten minutes (duration of observation) because ivabradine has no analgesic properties and skin incision could have falsely raised the heart rate and blood pressure giving false results.

In our study, there was not a very significant increase in the hemodynamic parameters in response to laryngoscopy and intubation in the Test group, when compared to the control group and the minimal raise also returned to baseline immediately within a minute. Whereas in the control group the baseline reading itself was high and the increase in the haemodynamic especially the pulse rate though decreased to some extent it was significantly being maintained above the normal value.
The principal advantage of using ivabradine during the study is:

1. Good attenuation of heart rate response.[14]
2. Mild attenuation of blood pressure response.
3. There was good intraoperative protection against abnormal cardiovascular response in the perioperative period.
4. There was good response to the pressor effects during extubation also.
5. The drug has minimal side effects. No side effects were observed during the study.
6. The drug is easily available, easy to administer, cost is also reasonable (rs.10/5 mg tablet).

King et al in 1951 described pressor response to laryngoscopy and intubation in anaesthetized patients.

Prys Roberts et al in 1970 by their series of studies concluded that the reflex responses occur in both treated and untreated hypertensive patients, and that the risk is more in the later. They have suggested the use of β-blockers to attenuate responses.[15] In 1971 they have identified myocardial ischemia as a complication following laryngoscopy and intubation.

Constance H.K. in 1977 described that the reflex response may be hazardous in patients of hypertension, myocardial insufficiency or cerebrovascular disease; but may not be the same in a healthy person.

J. Gilbert Stone et al in 1988 stated that the exaggerated haemodynamic responses undoubtedly cause a large increase in myocardial oxygen demand.

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Beta- receptor blocking prophylaxis was given by Pierce Fox, John Sear Lynne in 1988, for patients with hypertension and ischaemic heart disease and concluded that reflex response to laryngoscopy and intubation was blocked by Labetalol effectively than atenolol or oxprenolol.

Wang et al in 1994 studied the effectiveness of bolus dose of esmolol in attenuating the hemodynamic responses undergoing surgery under general anesthesia.

STUDIES ON IVABRADINE:

CORONARY ARTERY DISEASE: The BEAUTIFUL study[16] has shown that in coronary patients with a heart rate more than 70 bpm, ivabradine significantly reduces the risk of:

- Coronary events by 22% (P=0.023).
- Fatal and nonfatal myocardial infarction by 36% (P=0.001).
- Coronary revascularization injuries (reperfusion injuries) by 30% (P=0.016).

CHRONIC HEART FAILURE: In the SHIFT study[17,18] ivabradine significantly reduced the risk of the primary composite endpoint of hospitalization for worsening heart failure or cardiovascular death by 18% (P<0.0001) compared with placebo on top of optimal therapy. These benefits were observed after 3 months of treatment. SHIFT also showed that administration of ivabradine to heart failure patients significantly reduced the risk of death from heart failure by 26% (P=0.014) and hospitalization for heart failure by 26% (P<0.0001).

The improvements in outcomes were observed throughout all pre-specified subgroups: female and male, with or without beta-blockers at randomization, patients below and over 65 years of age, with heart failure of ischemic or non-ischemic etiology, NYHA class II or class III, IV, with or without diabetes, and with or without hypertension.

The results of the International Trial on the Treatment of angina with Ivabradine vs. Atenolol (INITIATIVE) have just been published.[19] This randomized, double-blind study compared ivabradine with atenolol over 4 months in 939 patients with stable angina pectoris and documented coronary artery disease. Patients received either ivabradine 5 mg twice daily for 4 weeks increased to 7.5 mg twice daily for a further 3 months, or atenolol 50 mg once daily for 4 weeks increased to 100 mg once daily for a further 3 months.

At 4 months, total exercise duration on a treadmill ETT at trough drug activity increased by 86.8 s with ivabradine 7.5 mg and 78.8 s with atenolol 100 mg.

At the rough drug activity, ivabradine 7.5 mg was not inferior to atenolol for all primary and secondary analyses including time to limiting angina, time to angina onset and time to 1-mm ST-segment depression at month 4 ($p < 0.0001$).

Ivabradine was not inferior to atenolol at peak drug activity at month 1 for all parameters. By month 4, non-inferiority of ivabradine 7.5 mg to atenolol was retained for all parameters except time to 1-mm ST-segment depression. Visual symptoms occurred at a similar rate to that seen in the first study.

These results indicate that by lowering heart rate, ivabradine is at least as effective as atenolol in patients with stable angina pectoris. Extension of the analysis in patients aged over 65 years confirmed that the efficacy of ivabradine is maintained in older patients.

Absence of fall of blood pressure in all the above patients was of great

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Advantage and hence the enhanced safety associated with the drug.

Ivabradine has been very useful in controlling the hemodynamics particularly the heart rate in all types of patients especially in patients where beta blockers are contraindicated such as asthmatics and diabetics (4 out of 25 in ivabradine group were diabetic and 2 out of 25 patients gave history of allergic rhinitis).

It is more useful in patients with diabetes and bronchial asthma where beta blockers are either contraindicated or have limitations regarding their use.[20]

Even in cases of difficult intubation where the intubation took longer time (>20 seconds), ivabradine was extremely useful in getting back the heart rate to baseline levels quickly. This aspect is a definite advantage in patients where the hemodynamic responses may not be thoroughly blunted.

Bêta blockers have been traditionally used in patients to control the heart rate. Though they are very good drugs in controlling the heart rate, they also have a lot of side-effects which require caution during their use like bradycardia, masking of hypoglycemic response, blunting of the normal response to hypotension i.e. tachycardia etc..

Ivabradine is one unique drug which can be used very safely in diabetic patients as it does not unmask the signs of hypoglycemia and has negligible influence on altering blood glucose levels.

During our study on ivabradine, there were no abnormal hemodynamic responses in any of our patients by way of profound bradycardia or hypotension.

Ivabradine does not prevent increases in blood pressure due to laryngoscopy and endotracheal intubation. But the increase in blood pressure seen during laryngoscopy and intubation return to the baseline values within reasonable time (around 3 minutes).This is a definite advantage and justification for using the drug as a routine in anesthesia practice.

It's already proven efficacy in critical conditions like ischemic heart disease, angina pectoris, diabetes, congestive heart failure, obstructive cardiomyopathies, myocardial infarction, ability to reduce the size of an infarct in an acute M.I etc., makes it an ideal drug for use before induction of anaesthesia.[21]

The drug as seen from our study can be used even in normotensive patients to prevent unwarranted and unwanted tachycardia commonly witnessed during general anesthesia techniques.

Ivabradine is an extremely simple, safe, economical and easy to use drug for achieving satisfactory hemodynamic goals during anesthesia at induction, intubation, per-operative and also the immediate postoperative period.

CONCLUSION:

1. Ivabradine is an extremely useful drug to prevent abnormal increase in heart rate seen during laryngoscopy and endotracheal intubation.
2. Though fully not effective, it also minimizes the extent of hypertension seen during laryngoscopy and endotracheal intubation and helps in return of blood pressure to the baseline values within a short period of time (around 3 minutes after endotracheal intubation).
3. Its proven safety in conditions like ischaemic heart disease, angina pectoris, diabetes mellitus, allergic bronchitis and asthma, obstructive cardiomyopathies enhances our claim for its routine use in all patients at risk for hypertension and tachycardia during laryngoscopy and endotracheal intubation.
4. The benefits on haemodynamics extend over during extubation of patients and help in a stable haemodynamic status in the immediate post-operative period.

5. In routinely administered clinical dose as practiced in our study there were no adverse side effects on pulse rate, blood pressure and even on the lung mechanics.

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