Original Article

To Evaluate The Use Of Ivabradine In Prevention Of Hemodynamic Response To Laryngoscopy And Intubation

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Abstract

An increase in blood pressure and increased heart rate is commonly associated with laryngoscopy and intubation if done before attaining an adequate depth of anaesthesia. However failure to counteract the catecholamine response to intubation may have disastrous consequences. In patients with hypertension, increased intracranial pressure, aneurysmal vascular disease, and diseased cerebral vasculature or ischemic heart disease, additional care has to be taken while intubating. Hence, we performed a study to optimize the hemodynamics prior to laryngoscopy and intubation.

METHODS AND MATERIALS-

This is a prospective randomized controlled trial that included 60 patients divided into two groups- I and II. The study included of patients aged 18-60 years, both males and females, weighing between 50-70 kgs, belonging to ASA class I/II. The study excluded those patients with Hypersensitivity to ivabradine, Resting heart rate below or equal to 60 beats per minute, SA and AV block patients, Patient on antihypertensive medications, Patient with severe hepatic insufficiency and Pregnant females and lactating mothers.

Drug—Ivabradine in 2.5mg and 5 mg doses

Each patient underwent a thorough preanaesthetic examination and all routine laboratory test including hemogram, coagulogram, biochemical indices, X-Ray chest and ECG and other special investigations if necessary.

RESULTS-

There was a statistically significant difference in the SBP, MBP and DBP at 30 and 45 minute duration post administration of IVABRADINE 5 mg when compared to 2.5 mg. However, there was no significant alteration in SpO2 and EtCO2.

CONCLUSION-

IVABRADINE is a safe drug administered prior to the laryngoscopy and intubation as it ensures optimal hemodynamics throughout the procedure.

INTRODUCTION –

The definite mechanism for the reaction to intubation is not properly described but there are studies confirming adrenergic and cholinergic association to intubation response. It is a brief effect that stays from 30 seconds after intubation and continues up to 10 minutes after that (1). The resultant response of this involuntary rise is an elevated Blood pressure (BP), heart rate (HR), pulmonary artery wedge pressure, and

low ejection fraction.

An increase in blood pressure and increased heart rate is commonly associated with laryngoscopy and intubation if done before attaining an adequate depth of anaesthesia since the 1950s. There is a net increase in blood pressure by 40-50% and heart rate by 20% because of the stress response occurring due to laryngoscopy and intubation. It is well explained that rising plasma concentrations of catecholamines which can lead to myocardial ischaemia and arrhythmias. (2) However failure to blunt the response to intubation may have disastrous consequences in patients with hypertension, increased intracranial pressure, aneurysmal vascular disease, and diseased cerebral vasculature or ischaemic heart disease. (3)

Complications that might arise because of cardiovascular responses to laryngoscopy and intubation are acute left ventricular failure, dysarrhythmias, intracranial bleed and pulmonary edema. Convulsions may be precipitated in patients with eclampsia. Various strategies have been applied to attenuate these responses in high risk individuals, including the use of Ivabradine (4). Being different than beta locker, it decreases the heart rate without significantly changing the heamodynamics in compromised patients. By not allowing the heart rate to increase, It conserves the oxygen reserves of the myocardium and reduces the myocardium oxygen demand. (5)

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 measures 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.

Methods and materials

This is a prospective randomized controlled trial in Mahatma Gandhi hospital in Jaipur between July 2015 to September 2017. IEC clearance was obtained prior to the study. Written informed consent was obtained from all participants. The study included 60 patients divided into two groups- I and II. The study included of patients aged 18-60 years, both males and females, weighing between 50-70 kgs, belonging to ASA class I/II. The study excluded those patients with Hypersensitivity to ivabradine, Resting heart rate below or equal to 60 beats per minute, SA and AV block patients, Patient on antihypertensive medications, Patient with severe hepatic insufficiency and Pregnant females and lactating mothers.

Drug—Ivabradine in 2.5mg and 5 mg doses

Each patient underwent a thorough preanaesthetic examination and all routine laboratory test including hemogram, coagulogram, biochemical indices, X-Ray chest and ECG and other special investigations if necessary.

Patients were randomly divided into two groups of 30 each with the help of a computer-generated table of random numbers.

Group I: Patients taking 2.5 mg of IVABRADINE Group II: Patients taking 5 mg of IVABRADINE

Group I and Group II patients were given oral ivabradine 2.5mg and 5 mg in the morning of surgery 1 hr before with sips of water.

All the patients in study group were premedicated with 1 mg of lorazepam in night and on the morning of surgery. In the operating room standard 5 leads ECG, non-invasive blood pressure and pulse oximetry will be attached and base line parameters will be noted. Injection midazolam 1 mg and fentanyl 2µg/kg IV was given. After 1 minute, induction was performed with propofol 2mg/kg IV followed by rocuronium 0.8mg/kg IV as muscle relaxant. Endotracheal intubation was performed after 90 seconds of IV rocuronium. 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.

Hemodynamic parameters was recorded at 0, 1, 3, 5, 10 minute after intubation and every 5 minute therafter, till the end of surgery.

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.

Results-

Both the groups were evenly matched for age distribution between the patients (p=0.938). The average age of patients receiving ivabradine 2.5mg was
34.3 years (Range 25-60 years) while for the patients receiving 5mg was 34.6 years.(range 24-60 years).

	Mean	**±SD**	**P value**
Group I	34.33	13.45	0.938
Group II	34.60	13.10	

SEX DISTRIBUTION

19 males and 41 females were enrolled in the study. There was no statistical difference in sex ratio of the two groups (p=0.405)

Sex Distribution

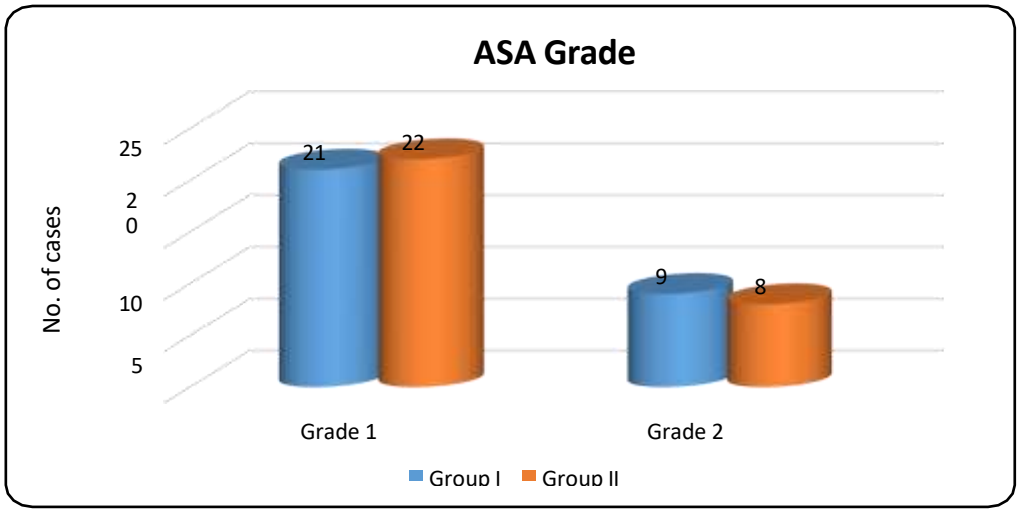
	Group I		**Group II**		**P value**
	No.	**%**	**No.**	**%**	
Male	8		11		0.405
Female	22		19		
Total	30		30		

ASA STATUS

The group 1 included 21 patients in ASA grade 1 and 9 patients in ASA grade 2. Composition of the group 2 was 22 patients in ASA grade 1 and 8 patients in ASA grade 2. There was no significant difference in ASA status of the two groups of patients.

ASA Grade

	Group I	Group II	P value
Grade 1	21	22	0.774
Grade 2	9	8	
Total	30	30	



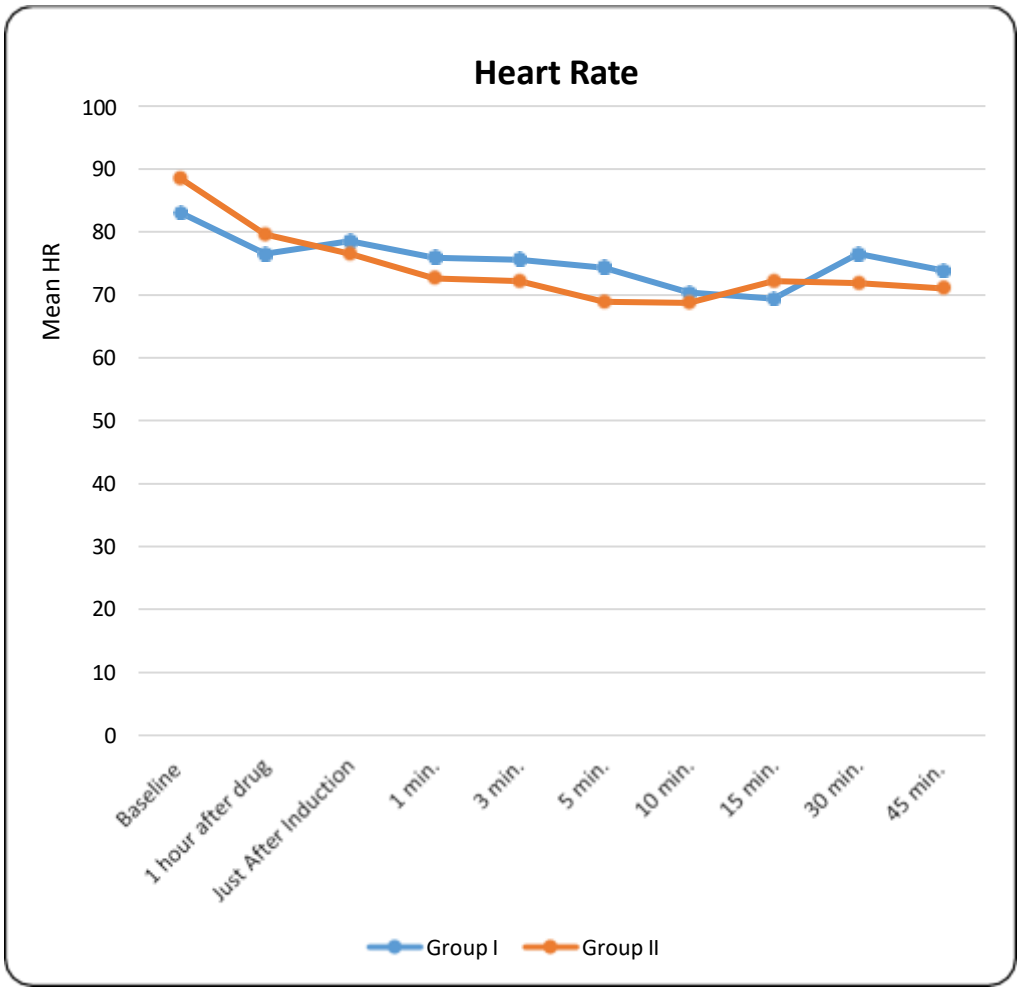
VITAL PARAMETERS

1) HEART RATE

Heart Rate was nearly similar between the two groups except at 1st minute and 3rd minute after intubation and laryngoscopy which was significantly reduced in group 2 than group 1. p value for difference @ 1st minute is 0.015 an @ 3rd minute is 0.028

Heart Rate

	Group I		Group II		P value
	Mean	**±SD**	**Mean**	**±SD**	
Baseline	83.03	8.12	88.47	10.42	0.0280
1 hour after drug	76.50	6.37	79.60	9.41	0.140
Just After Induction	78.53	5.78	76.50	6.37	0.200
1 min.	75.93	5.69	72.63	4.44	0.015
3 min.	75.60	5.35	72.17	6.43	0.028
5 min.	74.33	7.51	68.90	5.92	0.002
10 min.	70.37	5.26	68.73	5.69	0.252
15 min.	69.40	4.50	72.17	6.43	0.058
30 min.	76.50	6.37	71.83	7.33	0.010
45 min.	73.87	7.97	71.03	7.13	0.152



2) SYSTOLIC BLOOD PRESSURE

Mean SBP was also similar in the two groups. Average SBP is 115.47 in group 1 while it was 114.83 in the group 2.

	Group I		Group II		P value
	Mean	±SD	Mean	±SD	
Baseline	118.77	7.47	119.33	8.36	0.782
1 hour after drug	112.07	8.75	113.13	7.61	0.616
Just After Induction	107.37	6.99	107.23	7.54	0.943
1 min.	107.13	6.16	107.27	8.60	0.945
3 min.	106.67	5.36	109.97	6.54	0.036

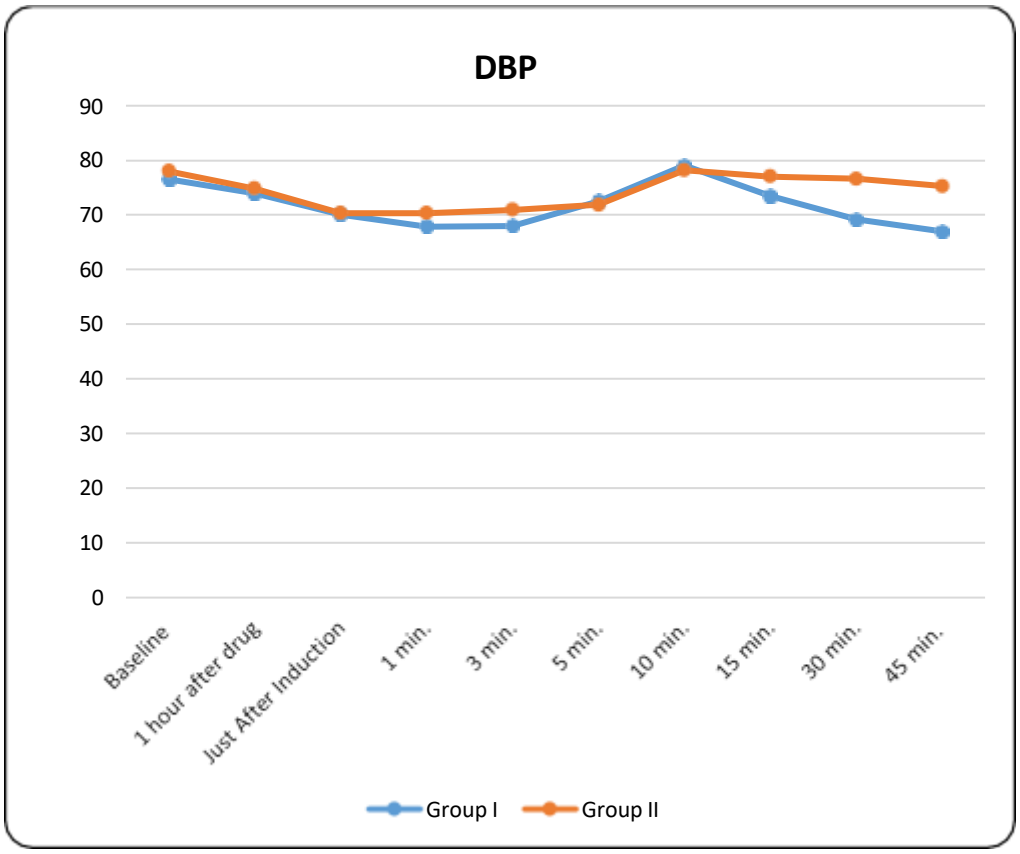
5 min.	115.07	7.85	116.10	3.94	0.521
10 min.	123.87	5.85	124.17	5.20	0.834
15 min.	117.47	5.92	120.13	8.35	0.159
30 min.	108.20	7.16	118.50	8.00	0.000
45 min.	105.47	6.32	112.50	8.88	0.0008

3) DIASTOLIC BLOOD PRESSURE

Mean DBP was also similar in the two groups. Average DBP was 71.77 in the group 1 while it was 74.35 in the group 2.

DBP

	Group I		Group II		P value
	Mean	±SD	Mean	±SD	
Baseline	76.57	7.67	78.00	9.65	0.526
1 hour after drug	74.00	7.62	74.87	8.30	0.675
Just After Induction	70.07	7.57	70.33	8.43	0.897
1 min.	67.90	6.87	70.33	8.59	0.230
3 min.	68.00	5.59	70.97	8.90	0.127
5 min.	72.50	6.99	71.87	8.95	0.761
10 min.	79.07	6.91	78.20	7.05	0.632
15 min.	73.47	8.15	77.03	8.26	0.097
30 min.	69.17	7.57	76.63	7.55	0.00032
45 min.	67.00	7.51	75.27	9.43	0.00040



4) MEAN ARTERIAL PRESSURE

Mean Arterial Pressure was also similar in the two groups. Average MAP was 85.13 in the drug group 1 while it was 87.20 in the group 2

MAP

	Group I		Group II		P value
	Mean	±SD	Mean	±SD	
Baseline	89.40	8.29	91.57	9.55	0.352
1 hour after drug	86.63	7.50	87.10	6.67	0.799
Just After Induction	82.13	7.55	81.03	7.76	0.580

1 min.	80.70	5.93	82.03	7.88	0.461
3 min.	81.40	4.90	83.53	8.16	0.224
5 min.	87.40	6.28	86.37	7.48	0.564
10 min.	93.90	5.16	93.47	5.06	0.743
15 min.	88.23	6.83	90.73	8.76	0.222
30 min.	82.00	7.19	89.33	8.56	0.00067
45 min.	79.57	6.80	86.87	8.15	0.0003

5) SPO2

Spo2 remained same in both the groups, there was a very minimal difference.

	Group I		**Group II**		**P value**
	Mean	**±SD**	**Mean**	**±SD**	
Baseline	99.57	0.50	99.33	0.48	0.0713
1 hour after drug	99.57	0.50	99.33	0.48	0.0713
Just After Induction	99.57	0.50	99.33	0.48	0.0713
1 min.	100.00	0.00	99.33	0.48	0.000
3 min.	100.00	0.00	100.00	0.00	-
5 min.	100.00	0.00	100.00	0.00	-
10 min.	100.00	0.00	100.00	0.00	-
15 min.	100.00	0.00	100.00	0.00	-
30 min.	100.00	0.00	100.00	0.00	-
45 min.	100.00	0.00	100.00	0.00	-

6) EtCO2

Mean EtCO2 was also similar in the two groups. Average EtCO2 was 28.51 in both the groups

	Group I		Group II		P value
	Mean	**±SD**	**Mean**	**±SD**	
Just After Induction	35.50	1.07	35.50	1.07	1.00
1 min.	35.50	1.07	35.50	1.07	1.00
3 min.	35.50	1.07	35.87	1.22	0.2221
5 min.	35.87	1.22	35.50	1.07	0.2226
10 min.	35.50	1.07	35.87	1.22	0.221
15 min.	35.87	1.22	35.50	1.07	0.2226
30 min.	35.50	1.07	35.87	1.22	0.221
45 min.	35.87	1.22	35.50	1.07	0.2226

Patient characteristic data will be analysed with a one-way ANOVA for continuous variables and x2 test for categorical variables. Two-way ANOVA will be applied to evaluate the changes in HR and BP before and after injection between the groups. The package SPSS 20.0 (IBM SPSS statistics) will be used for statistical analysis. P value <0.05 will be considered significant.

Discussion

In the early 1940s, Reid and Brace were the first to report heamodynamic changes due to laryngoscopy and endotracheal intubation during induction of anaesthesia in 1940 (6), these reflexes included increase in heart rate and arterial pressure i.e SBP, DBP, MAP which peak in about 30-40 seconds post laryngoscopy and intubation.

Patients who have compromised cerebral and cardiovascular systems have very serious and life endangering effects due these short term changes in pressures and heart rate. To abolish these responses due to laryngoscopy and endotracheal intubation many different methods have been employed such as superior laryngeal nerve block with topical anaesthetics, use of lignocaine spray intractracheally, use of intravenous lignocaine, inducing deep plane of anaesthesia with inhalational anaesthetics, cardiovascular drugs like beta blockers, alpha blockers, alpha-beta blockers such as labetelol, nitropruside, nifidepine, nitroglycerine either by oral, intravenous or intranasal route, use of narcotic drugs like fentanyl, remifentanyl, morphine.

In this present study, there was very insignificant increase in the hemodynamic parameters in response to laryngoscopy and intubation in the Test group ie one in which 5mg dose of ivabradine was used when compared to the control group in which 2.5mg dose of ivabradine was used and the minimal raise also returned to baseline immediately within three minutes. 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.

Benefits of using Ivabradine were – significant decrease in heart rate[14-20] minimal decrease in blood pressure , good perioperative shielding averse to unusual cardiac effects, sturdy reaction to stress response at the time of extubation, nominal adverse reactions. Dose used in our study showed no adverse reactions. Also we contemplated that ivabradine can be used in stable patients with normal pressures to attenuate undesireable tachyarrhythmias usually observed at the time of inducing general anaesthesia.

King et al (7) in 1951 explained the stress response due to laryngoscopy and intubation in patients undergoing general anaesthesia. Constance H.K (67). in 1977 expressed that the stress response can be erratic in patients suffering from hypertension, myocardial insufficiency or cerebrovascular disease; but might not be seen in a healthy person. J. Gilbert Stone et al (8) in 1988 confirmed that the extensive stress responses apparently cause an extravagant rise in oxygen requirements of myocytes.

During this study on ivabradine, there were no abnormal hemodynamic responses in any of our patients in form of bradycardia or hypotension and the increase in blood pressure seen during laryngoscopy and intubation has been found to return to the baseline values within reasonable time (around 3 minutes).This is a definite advantage for using the drug as a routine in anaesthesia practice.

The present study showed findings similar to that of that done by Raghuram and team (15), where patients received 5 mg Ivabradine, and there was no significant increase in haemodynamic parameters.

Conclusion-

Ivabradine can also be used even in normotensive patients to prevent unwanted tachycardia commonly witnessed during general anaesthesia techniques. Thus, inferring that a 5mg dose of ivabradine is adequate and safe to be used in regular anaesthesia practice.

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