

Attenuation of Hemodynamic Response to Laryngoscopy and Endotracheal Intubation by using Oral Ivabradine

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Abstract

Introduction: Laryngoscopy gives rise to a stress response that is seen as rise in heart rate and blood pressure and as dysrhythmia. Such changes are at peak immediately after intubation and can be dangerous for those having already limited or compromised cardiovascular reserve. They can lead to increased risk of myocardial infarction (MI), stroke, congestive cardiac failure or sudden death. **Aims and Objectives:** To study the effect of oral Ivabradine in attenuating the hemodynamic stress response to laryngoscopy; and to endotracheal intubation and extubation. **Materials and Methods:** A randomized double blinded study was done. Total number of 140 patients (adult patients undergoing ENT surgery) were randomly taken into two Groups. The first group was labelled as Test Group (A) and the second group was called Control Group (B). Each group had 70 patients. The Test group (A) received 5 mg oral Ivabradine and the Control group (B) received placebo. Patients were monitored for hemodynamic changes as per the protocol. **Result:** Mean heart rate, SBP, DBP and MAP reading at intubation, post-intubation period till 10 mins, at extubation and till 10 minutes post-extubation were significantly less in test group i.e. in patients who received oral Ivabradine as compared to control group ($p < 0.05$). **Conclusion:** We conclude that Ivabradine is an extremely useful drug to prevent abnormal tachycardias during the procedure of laryngoscopy and intubation. Its stabilizing effect of haemodynamics also extends up to extubation and immediate post-operative period.

Keywords: Ivabradine; Heart Rate; Diastolic Blood Pressure; Systolic Blood Pressure; Mean Arterial Pressure.

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Introduction

Endotracheal intubation is a very common procedure, where the anesthesiologists have an important role to play.

Stress response with laryngoscopy manifest as tachycardia, hypertension and dysrhythmias and

may have deleterious respiratory, neurological and cardiovascular effects¹. These changes are maximum immediately after intubation and lasts for 5-10 minutes.

These effects are generally well tolerated by overall healthy patients but can be lethal to patients with preexisting conditions such as coronary

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artery disease, recent myocardial infarction, hypertension, geriatric population, pre-eclampsia, and cerebrovascular pathology such as tumours, aneurysms or increased intracranial pressure and are at increased risk of morbidity and mortality.²

Geriatric and elderly patients are more susceptible to coronary artery disease and cerebrovascular disease as they have elevated baseline blood pressure, making them especially susceptible to variations in blood pressure, and heart rate during the procedures of laryngoscopy and endotracheal intubation, which can become critical for patients with compromised cardiovascular reserve with the resultant risk of myocardial infarction (MI), stroke, congestive heart failure or sudden death.³

Ivabradine also known as a cardiogenic agent is a highly selective inhibitor of 'I_f' channels which causes a reduction in the slope of spontaneous depolarisation. This results in an increase in the time interval between successive action potentials in the SA node, which in turn leads to slowing of heart rate.

Ivabradine slows down the heart rate but it does not cause sudden fall in blood pressure and for this reason it is desirable to use it in patients with pre-existing heart conditions like angina pectoris, coronary artery disease, heart failure, obstructive cardiomyopathies and other conditions where the myocardial perfusion is reduced.⁴

The α -2 receptors are present at various sites in peripheral and central nervous system, in visceral organs such as liver, kidney, pancreas, in eyes, the media of vessel walls, and also in platelets.⁵

It is difficult to classify the α -2 receptors on the basis of anatomical location as these receptors are present in presynaptic, postsynaptic and extrasynaptic locations.⁶

These receptors are divided into three subtypes and each type has unique actions of α -2 receptors. Within the CNS, the subtype A receptors are more common and are responsible for the sedative, analgesic and sympatholytic effect. The peripheral vessels and vasculature house the subtype B receptors that are responsible for the short term hypertensive response. The CNS also has subtype C receptors which play a role in anxiolysis.⁷

The α -2 adrenergic receptor mediates its effect by activating guanine-nucleotide regulatory protein (G proteins) which modulate cellular activity by signalling a second messenger system, which when activated leads to inhibition of adenylate cyclase which in turn, results in decreased formation of 3',5'-cyclic adenosine monophosphate (c-AMP).

This leads to hyperpolarization of the excitable cell membranes and provides effective means of suppressing neuronal firing. Stimulation of α -2 receptor also suppresses calcium entry into the nerve terminal, which may be responsible for this inhibitory effect on secretion of neurotransmitters.⁸

Aims and Objectives

1. To study the effect of oral Ivabradine on the hemodynamics (Heart rate, SBP, DBP and MAP) at the time of laryngoscopy and endotracheal intubation and also during extubation, in patients undergoing surgical procedures under general anesthesia.
2. To study the incidence of side effects (bradycardia, hypotension) and complications, if any, due to study drug.

Material and Methods

Study Area

Department of Anesthesia, Shri Mahant Indresh Hospital, the associated hospital of Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun (Uttarakhand).

Study Population

Adult patients undergoing ENT Surgery at our hospital

Study Design

A randomized double blinded study.

Sample Size

A total of 140 patients were studied. They were randomly put in two groups labelled as Test group and Control so that each group had 70 patients. The opaque, sequentially numbered sealed envelopes were stored in the preoperative room. Randomization of the patients to one of the 2 treatment arms was done using computer generated random numbers. Each patient picked up an envelope which contained a folded card. Those marked with 'A' were randomized to receive 5 mg oral ivabradine and those marked received 'B' placebo (sugar coated tablet).

Group-A or the Test Group: Had 70 patients, and they were given oral Ivabradine, 5 mg tab one hour before intubation.

Group-B or the Control Group: Had 70 patients, and they were given placebo (sugar coated tablet) one hour before intubation.

Study Duration

Dec 2016 - May 2018

Inclusion Criteria

Adult patients undergoing ENT Surgery, ASA Grade-1 and Grade- 2 and Age group of 20-50 years

Exclusion Criteria

Patients who refused to participate in the study, patients with low base line heart rate of less than 60 beats per minute, base line SBP <100 mm Hg, those having abnormal ECG readings, patients with previous history of angina or chest pain, or palpitations or history of syncope or any visual disturbances.

Patients already taking calcium channel blockers, azole antifungals, antiretroviral drugs, and macrolide antibiotics were excluded.

ASA Grade 3 and 4 were excluded.

Pregnant and breastfeeding females were excluded.

Patients with difficult intubation that took more than 20 seconds to intubate were also excluded.

Methodology

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

Intravenous cannulation with 18G cannula was done once the patients were shifted into the preoperative room and a drip of ringer lactate solution was started.

Premedication was done with Midazolam 1mg and Ondansetron 4 mg slowly intravenously, just before induction.

Injection fentanyl in a dose of 2 mcg/kg body weight was given as an analgesic.

Patient was connected to non- invasive blood pressure monitors, pulse oximeter probe and electrocardiographic leads. All patients were pre oxygenated with 100% oxygen for 3 minutes.

Injection Propofol (2 mg/kg body weight) was used for induction of patients.

Vecuronium 0.1 mg/kg intravenously was used to facilitate the intubation. The lungs were ventilated with 100% oxygen for 3 minutes.

For both the groups, intubation was timed at 60 minutes after Ivabradine pre-treatment. Intubation was performed with an appropriate size oral cuffed, portex endotracheal tube by the aid of Macintosh laryngoscope blade.

Care was taken to ascertain that the time taken for intubation did not exceed 20 seconds. Anesthesia was maintained with Vecuronium bromide 0.02 mg/kg top-up doses; inhalational agent Isoflurane and intermittent positive pressure ventilation with nitrous oxide and oxygen in the ratio of 60%: 40% using circle absorber system connected to the Anesthesia work station (Dräger Fabius plus).

Recording of hemodynamic parameters were done as the patient was being cleaned and draped followed by commencement of surgery.

The recording of hemodynamic parameters was taken throughout the intra operative period.

At the end of the surgery, neuromuscular blockade was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.008 mg/kg). All the patients were thoroughly followed in the post-operative period.

In the postoperative period, both the groups were checked for any incidence of adverse effects of Ivabradine for 4 hours.

Any incidence of severe bradycardia (Heart Rate <50 bpm) was treated with injection Atropine 0.6 mg intravenously stat and hypotension (BP < 90/60 mm hg) was treated with injection ephedrine 6 mg intravenously stat.

The parameters that were recorded were

Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure.

The above parameters were recorded at specific intervals as follows

Pre-operatively i.e. after premedication (for the basal line value).

At the time of induction/intubation, 1 minute after intubation 3, 5, 8 minutes and 10 minutes after intubation.

At the time of extubation, 1 minute after extubation, 3, 5, 8 minutes and 10 minutes after extubation.

Instruments Required

Anesthesia work station (Drager fabius plus) with circle absorber.

Multipara monitor for NIBP, SPO₂, heart rate, ECG, Resuscitatory equipments (Laryngoscope with Macintosh blade, oral cuffed portex endotracheal tube etc.)

Statistical Analysis

The quantitative data was represented as their mean ± SD. Categorical and nominal data was expressed in percentage. The t-test was used for analysing quantitative data, or else non parametric data was analyzed by Mann Whitney test and categorical data

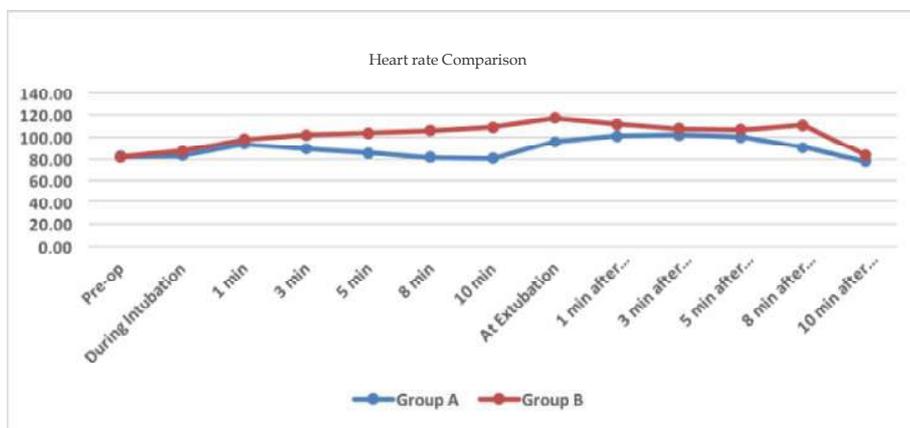
was analyzed by Chi-square test. The significance threshold of p-value was set at <0.05. SPSS software version 21 was used to analyse the data.

Results

Mean heart rate in test and control group were comparable at baseline i.e. pre-op period (82.47 vs 81.76/min; p=0.414). At intubation, post-intubation period till 10 mins, at extubation and till 10 minutes post-extubation, mean heart rate was significantly less in test group i.e. in patients who received oral Ivabradine as compared to control group (p<0.05). (Graph 1 and Table 1).

Table 1: Comparison of mean changes in heart rate between the two groups during the procedure

Heart Rate	Group	N	Mean	SD	p- value
Pre-op	A	70	82.47	4.46	0.414
	B	70	81.76	5.76	
During Intubation	A	70	83.04	6.06	<0.05
	B	70	87.23	6.26	
1 min	A	70	93.99	8.85	<0.05
	B	70	98.23	10.48	
3 min	A	70	89.27	8.84	<0.05
	B	70	102.10	8.56	
5 min	A	70	85.64	8.29	<0.05
	B	70	104.01	8.61	
8 min	A	70	81.40	7.20	<0.05
	B	70	105.93	10.81	
10 min	A	70	80.61	7.17	<0.05
	B	70	108.99	12.29	
At Extubation	A	70	96.00	14.86	<0.05
	B	70	117.49	18.30	
1 min after extubation	A	70	101.23	13.90	<0.05
	B	70	111.86	13.69	
3 min after extubation	A	70	101.97	12.85	<0.05
	B	70	107.89	10.18	
5 min after extubation	A	70	100.46	12.17	<0.05
	B	70	106.89	9.34	
8 min after extubation	A	70	90.91	7.81	<0.05
	B	70	111.00	9.34	
10 min after extubation	A	70	77.80	5.63	<0.05
	B	70	83.49	4.82	



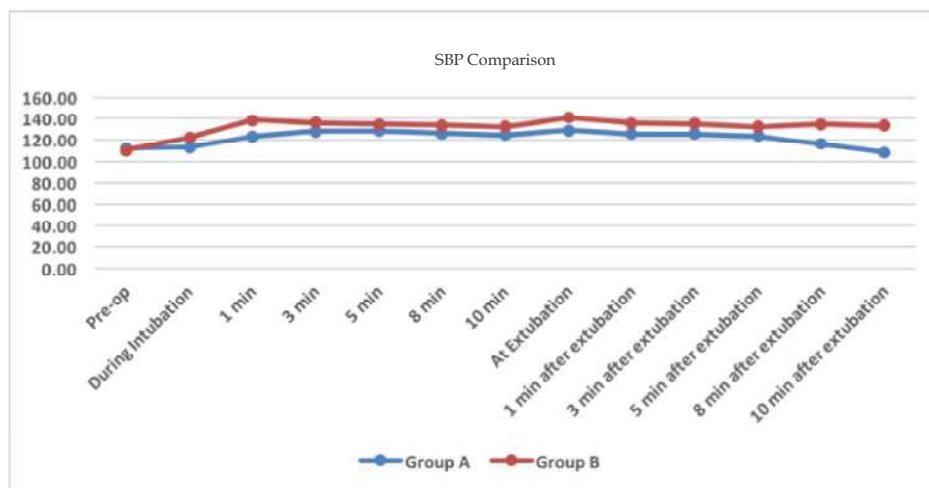
Graph 1: Comparison of mean changes in heart rate between the two groups during the procedure

Mean SBP in test and control group were comparable at baseline i.e. pre-op period (112.1 vs 110.47 mm Hg; $p = 0.69$). At intubation, post-intubation period till 10 mins, at extubation and

till 10 minutes post-extubation, mean SBP was significantly less in test group i.e. in patients who received oral Ivabradine as compared to control group ($p < 0.05$) (Graph 2 and Table 2).

Table 2: Comparison of mean changes in systolic blood pressure between the two groups during the procedure

Systolic Blood Pressure	Group	N	Mean	SD	<i>p</i> -value
Pre-op	A	70	112.10	8.83	0.69
	B	70	110.47	12.42	
During Intubation	A	70	112.97	6.11	<0.05
	B	70	122.43	10.28	
1 min	A	70	123.61	6.97	<0.05
	B	70	138.50	12.66	
3 min	A	70	128.01	7.74	<0.05
	B	70	135.81	8.35	
5 min	A	70	128.44	6.47	<0.05
	B	70	134.81	5.97	
8 min	A	70	126.33	6.39	<0.05
	B	70	133.89	4.56	
10 min	A	70	125.00	6.42	<0.05
	B	70	132.10	6.06	
At Extubation	A	70	129.13	4.97	<0.05
	B	70	140.57	7.85	
1 min after extubation	A	70	125.94	5.34	<0.05
	B	70	135.71	5.49	
3 min after extubation	A	70	125.57	5.49	<0.05
	B	70	135.17	4.37	
5 min after extubation	A	70	123.97	6.60	<0.05
	B	70	132.31	8.23	
8 min after extubation	A	70	116.57	10.50	<0.05
	B	70	134.63	16.06	
10 min after extubation	A	70	108.43	13.45	<0.05
	B	70	133.06	8.44	



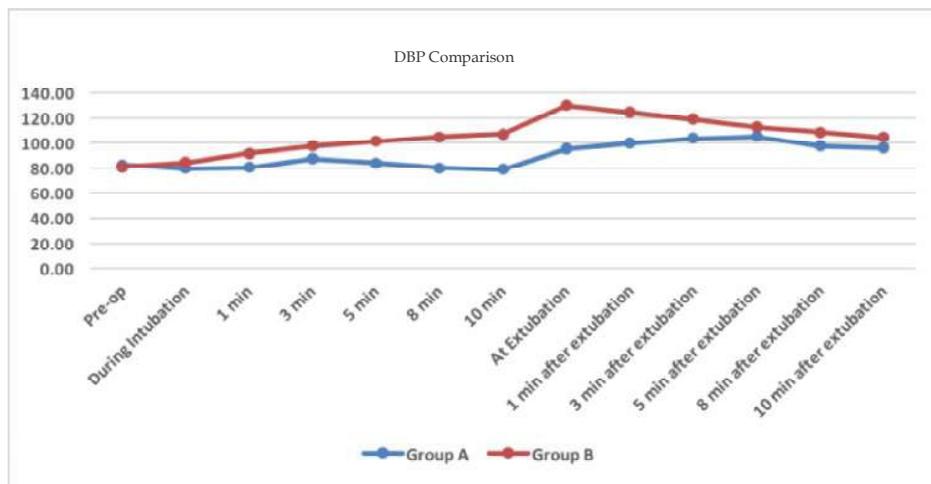
Graph 2: Comparison of mean changes in systolic blood pressure between the two groups during the procedure

Mean DBP in test and control group were comparable at baseline i.e. pre-op period (82.47 vs 80.71 mm Hg; $p = 0.21$). At intubation, post-intubation period till 10 mins, at extubation and

till 10 minutes post-extubation, mean DBP was significantly less in test group i.e. in patients who received oral Ivabradine as compared to control group ($p < 0.05$) (Graph 3 and Table 3).

Table 3: Comparison of mean changes in diastolic blood pressure between the two groups during the procedure

Diastolic Blood Pressure	Group	N	Mean	SD	p-value
Pre-op	A	70	82.47	5.75	0.57
	B	70	80.71	5.47	
During Intubation	A	70	79.51	6.81	<0.05
	B	70	84.27	7.01	
1 min	A	70	80.21	6.63	<0.05
	B	70	91.50	6.36	
3 min	A	70	87.43	7.03	<0.05
	B	70	97.21	8.92	
5 min	A	70	83.97	6.62	<0.05
	B	70	101.10	10.63	
8 min	A	70	80.17	5.92	<0.05
	B	70	104.74	12.94	
10 min	A	70	78.96	6.16	<0.05
	B	70	106.91	14.84	
At Extubation	A	70	95.17	16.65	<0.05
	B	70	129.66	17.72	
1 min after extubation	A	70	99.54	16.23	<0.05
	B	70	123.97	13.81	
3 min after extubation	A	70	103.57	15.99	<0.05
	B	70	118.74	11.02	
5 min after extubation	A	70	105.14	16.13	<0.05
	B	70	112.57	9.66	
8 min after extubation	A	70	97.13	10.98	<0.05
	B	70	108.37	10.42	
10 min after extubation	A	70	95.66	7.33	0.22
	B	70	104.26	6.07	



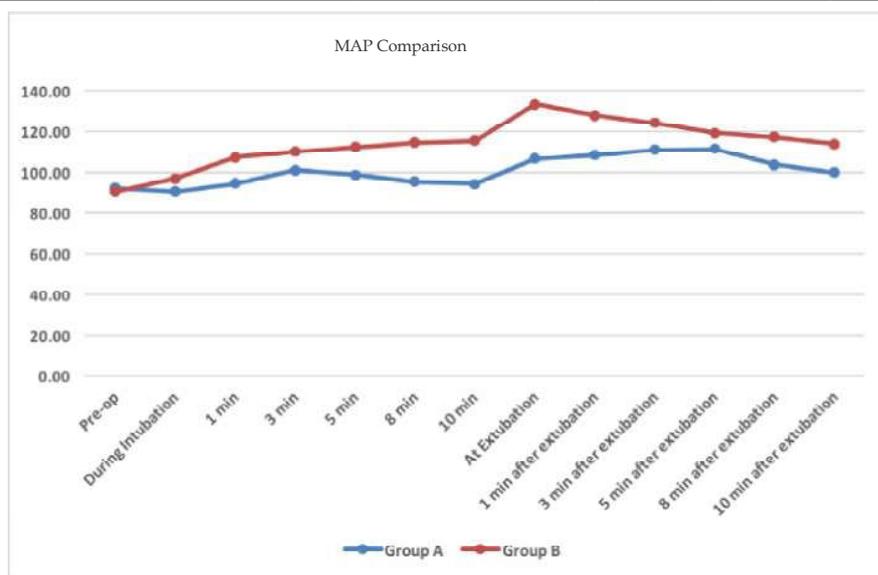
Graph 3: Comparison of mean changes in diastolic blood pressure between the two groups during the procedure

Mean arterial pressure in test and control group were comparable at baseline i.e. pre-op period (92.35 vs 90.63 mmHg; $p = 0.54$). At intubation, post-intubation period till 10 mins, at extubation

and till 10 minutes post-extubation, mean arterial pressure was significantly less in test group i.e. in patients who received oral Ivabradine as compared to control group ($p < 0.05$) (Graph 4 and Table 4).

Table 4: Comparison of mean changes in mean arterial blood pressure between the two groups during the procedure

Mean Arterial Pressure	Group	N	Mean	SD	p-value
Pre-op	A	70	92.35	5.41	0.54
	B	70	90.63	9.38	
During Intubation	A	70	90.67	4.91	<0.05
	B	70	96.99	7.23	
1 min	A	70	94.68	5.98	<0.05
	B	70	107.17	9.00	
3 min	A	70	100.96	5.71	<0.05
	B	70	110.08	6.86	
5 min	A	70	98.80	4.99	<0.05
	B	70	112.34	6.96	
8 min	A	70	95.56	4.90	<0.05
	B	70	114.46	6.95	
10 min	A	70	94.30	4.95	<0.05
	B	70	115.31	8.24	
At Extubation	A	70	106.49	10.56	<0.05
	B	70	133.30	22.43	
1 min after extubation	A	70	108.34	9.37	<0.05
	B	70	127.89	17.63	
3 min after extubation	A	70	110.90	7.85	<0.05
	B	70	124.22	13.12	
5 min after extubation	A	70	111.42	7.10	<0.05
	B	70	119.15	9.51	
8 min after extubation	A	70	103.61	8.91	<0.05
	B	70	117.12	7.96	
10 min after extubation	A	70	99.91	4.06	<0.05
	B	70	113.86	10.91	



Graph 4: Comparison of mean changes in mean arterial blood pressure between the two groups during the procedure

Discussion

The parameters of Mean heart rate, systolic and diastolic blood pressure and mean arterial pressure in test and control group were similar and comparable at baseline i.e. pre-op period ($p > 0.05$) (Table & Graph 1, 2, 3, 4).

After intubation, the placebo group showed a significant rise in heart rate and blood pressure ($p < 0.05$). Whereas, the Ivabradine group showed only a slight increase in heart rate (82.47 to 83.04/ min) and SBP (112.1 to 112.97 mm Hg) was observed post-intubation while a decrease was observed in DBP (82.47 to 79.51 mm Hg) and MAP (92.35 to 90.67 mm Hg) (Table & Graph 1, 2, 3, 4).

After induction and intubation a gap period of ten minutes (duration of observation) was taken wherein the surgeon was asked to wait and not start the surgery. Ivabradine has no analgesic properties and immediate skin incision if given would raise the heart rate and blood pressure giving false results.

In the post-intubation observation period of 10 mins, mean heart rate, SBP, DBP and MAP readings were significantly less in oral Ivabradine group as compared to the control group that was given placebo (p value < 0.05). (Table & Graph 1, 2, 3, 4).

Mean heart rate, SBP, DBP and MAP readings were found to be significantly less in oral Ivabradine group when compared to control group of placebo at extubation and post-extubation observation period of 10 mins ($p < 0.05$) (Table & Graph 1,2,3,4).

In a similar study by Kunwer R *et al.*⁹, mean heart rate which was 102.86 at preoperative time was gone up to 120.88 during intubation and it was still at 110.64/min. after 10 minutes, while in test group it was 82.6/min. which rose only up to 85.43 during intubation and came down to 73.46 at 10 minutes. Similar pattern was observed with mean SBP, DBP and MAP. The study results showed that haemodynamic parameters (during intubation and after 1, 3, 5, 8 and 10 min.) were found to be significantly lower in cases pre-treated with Ivabradine as compared to placebo.

Ibrahim *et al.*¹⁰ in their study evaluated oral Ivabradine and oral propranolol in achieving a hemodynamic stability in microlaryngoscopic surgeries. Study observed that the changes in blood pressure and heart rate in both groups were mild after intubation, laryngoscope fixation for surgery and extubation but the changes in Ivabradine group were significantly less than

the changes in propranolol group ($p < 0.05$). The authors concluded that premedication with oral Ivabradine in a dose of 5 mg or oral propranolol in a dose of 10 mg prior to microlaryngoscopic surgeries was effective in conferring good hemodynamic stability but that between the two, Ivabradine was more effective.

The advantage of Ivabradine noted in present study were – it gave good attenuation of heart rate response and blood pressure response during the process of intubation, the cardiovascular response in intraoperative period was smooth without any deviations, and also it was effective during extubation too.

No observed side effects with the dosage of Ivabradine were seen during the study. We thus conclude that Ivabradine is simple, safe, economical and easy to use drug that gives adequate and satisfactory haemodynamic stability during induction, laryngoscopy and intubation. Haemodynamic stability was also well maintained during intraoperative and immediate postoperative period.

Conclusion

We conclude that Ivabradine is an extremely useful drug and can be used to prevent tachycardia during laryngoscopy and intubation. Its stabilizing effect of haemodynamics also extends up to extubation and immediate postoperative period. There were no side effects seen with the dose of Ivabradine given in our study.

Recommendations

We recommend the routine use of Ivabradine to prevent the abnormal increase in heart rate and blood pressure seen during laryngoscopy and endotracheal intubation.

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Ethical Approval: granted

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