Original Article

DOI: 10.7860/JCDR/2022/59965.17226

Consequence and Prevention of Haemodynamic Stress Response during Laryngoscopy and Endotracheal Intubation with Oral Ivabradine- A Multicentric Randomised Controlled Study

Anaesthesia Section

ANKITA RUSHIK PATEL[1], HEENA SUNIL CHHANWAL[2], REKHA NILESH SOLANKI[3], PRATHEEBA NATARAJAN[4], NIKHIL KACHA[5]

ABSTRACT

Introduction: Laryngoscopy and intubation cause lots of haemodynamic changes which adversely affects the patient during the perioperative period. Various methods have been applied to reduce stress response in high risk patients. Ivabradine is a unique cardiotonic drug which reduces the heart rate without compromising blood pressure, specially in debilitating and severely ill patients.

Aim: To evaluate role of oral ivabradine in attenuating the haemodynamic stress response to laryngoscopy, intubation and extubation in patients undergoing surgical procedure under General Anaesthesia (GA) and to note the side-effects and its complications, if any.

Materials and Methods: A randomised controlled multicentric study was conducted in 200 American Society of Anaesthesiologists' (ASA)-I and II patients undergoing various surgery under general anaesthesia. The patients were randomly divided into two groups: group A (Test group, n=100) received 5 mg oral ivabradine one hour before intubation, group B (Control group, n=100) received placebo. The pulse rate, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were recorded at intubation and 10 minutes postintubation along with at extubation and postintubation period till 10 minutes. Patients were monitored for haemodynamic changes as per the protocol. Statistics analysis was done using Statistical Package of Social Science (SPSS) software version 21.0.

Results: Demographic findings were comparable in both groups. Heart rate (84.36±4.11 versus 114.19±12.4), SBP (120±10.5 versus 150±17.5), DBP (76.08±4.29 versus 113.2±10.6), MAP (91.3±6.7 versus 124.4±12.8) at 10 minutes postintubation decreased more in test group as compared to control group from baseline (p-value <0.005). Similarly, heart rate (84.13±2.06 versus 110.58±8.92), SBP (123.4±10.06 versus 150.8±13.1), DBP (84.08±2.02 versus 107±10.2), MAP (97.8±6.47 versus 122.06±9.7) at 10 minutes postintubation decreased significantly in test group as compared to control group from baseline (p-value <0.005).

Conclusion: Oral ivabradine is a very useful cardiotonic drug which facilitates the fluctuation in heart rate during laryngoscopy and endotracheal intubation.

Keywords: Attenuation, Cardiotonic drug, Diastolic blood pressure, Heart rate, Mean arterial pressure, Systolic blood pressure

INTRODUCTION

Stress response during laryngoscopy and endotracheal intubation leads to increase in heart rate, blood pressure and can cause harmful systemic effects [1]. In healthy patients compensatory mechanism is there, however, there are more chances of morbidity and mortality in pre-existing conditions like hypertension, coronary artery disease, recent myocardial infarction, raised intracranial pressure, geriatric population, preeclampsia, aneurismal vascular disorders and ischaemic heart disease [2].

Various techniques help in prevention of stress responses-using intravenous lignocaine, deeper plane of anaesthesia with inhalation agents or opioids, prostaglandins vasodilators, alpha adrenoreceptor antagonists, calcium antagonists, trinitroglycerin, and minimising the duration of laryngoscopy to <15 seconds [3].

Ivabradine inhibits the funny current ("If" channels) in sinoatrial nodal tissue that leads to decrease in the rate of diastolic depolarisation and consequently decreases heart rate without affecting blood pressure [4].

The patients with angina, coronary artery disease, cardiac failure, and obstructive cardiomyopathies are more susceptible to hypoxia. Oral ivabradine drug reduces the heart rate without reducing blood pressure [5,6]. Therefore, the oral ivabradine may be the choice of drug during GA due to its multiple benefits on myocardium. Oral ivabradine can be used in bronchial asthma and diabetic patients due to its advantages over beta blockers [7].

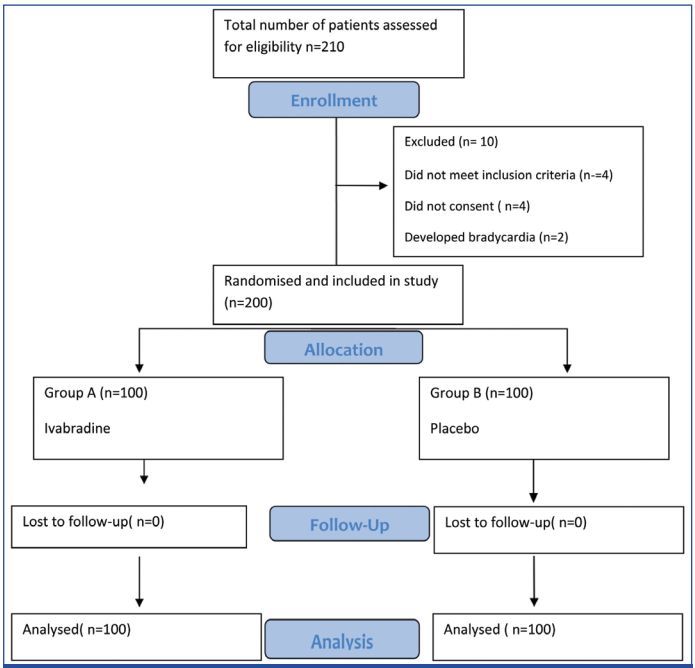
The aim of the present study was to evaluate the role of oral ivabradine in patients scheduled for surgery under GA. The primary outcome measures were the haemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure) while the secondary outcome measures were side-effects, if any.

MATERIALS AND METHODS

This randomised controlled multicentric study was conducted from December 2021 to June 2022 at the GCS Medical College, Hospital and Research Centre, Ahmedabad and Indira Gandhi Medical College, Research Institute, Puducherry. The ethical approval were obtained from the respective Institutional Ethics Committees, with the following reference numbers- GCSMC/EC/RESEARCH PROJECT/APPROVE/2021/327 (GCS Medical College, Hospital and Research Centre, Ahmedabad), and No386/IEC-33/IGMC&RI/PP-20/2022 (Indira Gandhi Medical College, Research Institute, Puducherry). This Clinical Trial Registry of India registration number is CTRI/2022/04/042188.

Patients written informed consents were obtained. A convenient sampling technique was used. Total 200 patients were enrolled and grouped into two, with 100 in each group [Table/Fig-1]. Patients were randomised into group A and group B with the help of computer-generated randomisation in opaque sealed envelopes, prepared by an independent paramedical nursing staff.

- Group-A (Test Group): 100 patients received oral ivabradine (5 mg) one tablet was given an one hour before laryngoscopy and intubation.
- Group-B (Control group): 100 patients received sugar coated tablet (placebo), administered one hour before laryngoscopy and intubation.



[Table/Fig-1]: CONSORT diagram.

Inclusion criteria: Patients in the age group of 20-50 years, undergoing surgeries in GA, ASA grade I and grade II, comprising both sexes were included.

Exclusion criteria: Patients who refused to give consent for this study, with baseline heart rate <60 beats per minute and SBP <100 mmHg, with abnormal electrocardiogram finding, with history of angina, chest pain, palpitations or syncope, with history of any visual disturbances, with liver and kidney dysfunction. Patients who already taking calcium channel blockers, azole antifungals, antiretroviral drugs and macrolide antibiotics and also pregnant and lactating mother were also excluded. Patients with difficult intubation that took more than 20 seconds were also excluded from this study.

Study Procedure

The premedication, induction agent and muscle relaxant were given as per the hospital protocols and following standard fasting guideline. A 18G intravenous cannula taken and intravenous crystalloid 10 mL/kg was started. All ASA basic standard monitoring were applied. Premedication with glycopyrrolate 0.2 mg, inj. midazolam 1 mg i.v. and ondansetron 4 mg were given slowly intravenously before induction. Inj. fentanyl 2 mcg/kg was given for analgesia. All patients were preoxygenated with 100% oxygen for 3 minutes. The patient was induced by injection propofol (2 mg/kg body weight). Intubation was done by using intravenous succinylcholine chloride 2 mg/kg after 60 minutes in ivabradine group-A and placebo in group-B.

Trachea was intubated with portex endotracheal cuffed tube and the time taken for intubation did not exceed 20 seconds. Anaesthesia was maintained with atracurium besaylate 0.5 mg/kg top-up doses; with combination of O_2+N_2O and inhalational agent. At the end of the surgery, patients were reversed with i.v. neostigmine (0.05 mg/kg) and i.v. glycopyrrolate (0.04 mg/kg) followed by extubation.

Haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, Oxygen saturation (SpO_2) and End-Tidal Carbon Dioxide ($ETCO_2$) were recorded at specific intervals as follows:

1. Preoperatively i.e. after premedication (for baseline values).
2. At the time of induction/intubation, 1 minute after, 3, 5, 8, and 10 minutes after intubation.
3. At the time of extubation, 1 minute after, 3, 5, 8, and 10 minutes after extubation.

All the patients were followed in postoperative period for four hours to check for any adverse effects of oral ivabradine.

STATISTICAL ANALYSIS

Statistics analysis was done using SPSS software version 21.0. Comparison of means between two groups was done using Student t-test or Modified t-test. Else, non parametric data was analysed by Mann Whitney test and categorical data was analysed by Chi-square test. Descriptive statistics was presented in form of numbers and percentages. The p-value <0.05 was taken as statistically significant.

RESULTS

The test and control groups were comparable regarding age, gender, weight, ASA grading, duration of surgery and time of medication, and intubation [Table/Fig-2]. SpO_2 and $EtCO_2$ were comparable in both groups. There were two patients in test group who developed bradycardia and were excluded from the study.

Parameters	Group A	Group B	p-value
Age (in years)	47.23±16.6	44.08±17.35	0.20
Gender (Male/Female)	73:27	69:31	0.53
Weight (kg)	65.71±7.7	64.97±5.87	0.65
ASA grading (I:II)	70:30	65:35	0.45
Duration of surgery	101.90±48.5	99.7±40.1	0.80

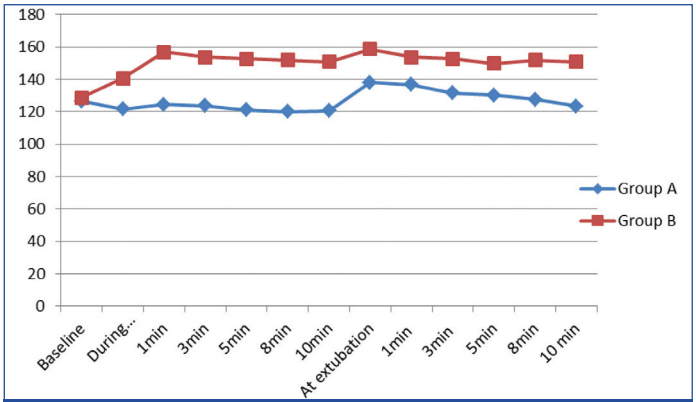
[Table/Fig-2]: Demographic data.

The mean heart rate in both groups were comparable at baseline, while during intubation and extubation it was significantly less in group A [Table/Fig-3].

Heart rate	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	88.44±3.37	90.86±13.7	0.07
During intubation	91.08±5.43	104.46±10.2	<0.05
1 min	96.32±3.67	102.88±9.19	<0.05
3 min	93.45±3.05	107.17±9.26	<0.05
5 min	89.78±3.68	109.12±9.56	<0.05
8 min	84.91±4.06	111.16±9.49	<0.05
10 min	84.36±4.11	114.19±12.4	<0.05
At extubation	95.65±5.09	127.37±11.7	<0.05
1 min	94.08±4.18	117.39±11.8	<0.05
3 min	91.96±3.17	111.81±12.0	<0.05
5 min	89.26±2.75	110.91±10.8	<0.05
8 min	85.30±2.80	115.24±9.45	<0.05
10 min	84.13±2.06	110.58±8.92	<0.05

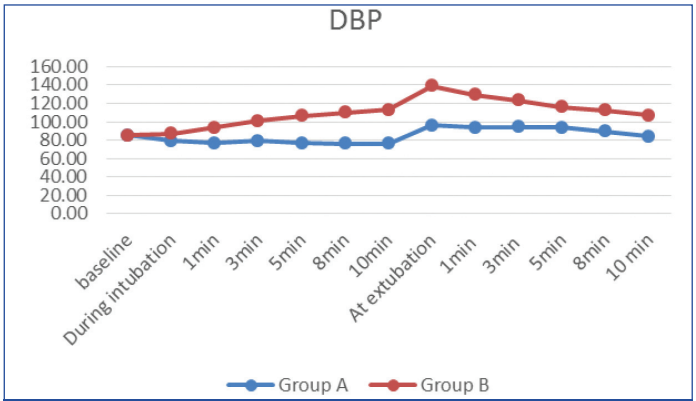
[Table/Fig-3]: Comparison of mean changes in heart rate between the two groups during the procedure.
The p-value <0.05 was taken as statistically significant

Mean SBP in both groups were comparable at baseline. At intubation, postintubation period till 10 minutes, at extubation and postintubation till 10 minutes, mean SBP was significantly less in group A as compared to B [Table/Fig-4].



[Table/Fig-4]: During intubation 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. At intubation, postintubation period till 10 minutes, at extubation and postintubation till 10 minutes, mean DBP was significantly less in group A as compared to B [Table/Fig-5].



[Table/Fig-5]: 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, while during intubation and extubation it was significantly less in group A [Table/Fig-6].

Mean arterial pressure	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	97.12±6.38	98.98±18.1	0.34
During intubation	93.26±6.53	105.65±13.5	<0.05
1 min	93.56±6.49	115.58±11.3	<0.05
3 min	94.70±6.51	118.81±12.8	<0.05
5 min	91.82±6.48	121.26±12.2	<0.05
8 min	91.05±6.57	122.82±12.1	<0.05
10 min	91.32±6.71	124.40±12.8	<0.05
At extubation	110.51±6.74	142.47±12.4	<0.05
1 min	110.05±6.47	136.32±12.7	<0.05
3 min	106.98±6.49	132.58±14.3	<0.05
5 min	106.81±6.42	127.31±12.7	<0.05
8 min	101.77±6.53	125.47±11.2	<0.05
10 min	97.88±6.47	122.06±9.77	<0.05

[Table/Fig-6]: Comparison of mean arterial blood pressure (MAP) between the two groups during the procedure.

There were no major side-effects of oral ivabradine but two patients had developed bradycardia and were managed adequately.

DISCUSSION

Cardiac and haemodynamic changes were first reported by Reid and Brace in 1940 during laryngoscopy and endotracheal intubation with conventionally used anaesthetic techniques. The sympathetic reflex including increase in heart rate and blood pressure in anaesthetised patients were usually peak after 30-45 seconds of laryngoscope and intubation. These transient changes may be serious and life threatening in patients with cardiovascular and cerebral disorder [2].

Ivabradine was approved by the European Medicines Agency in 2005 and by the United States Food and Drug Administration in 2005 [8]. However, ivabradine is indicated for symptomatic treatment of chronic stable angina pectoris with normal sinus rhythm in patients who can not take beta blocker and also it's being used off label in the treatment of inappropriate sinus tachycardia [9]. Initial oral ivabradine doses of 2.5 mg twice a day started and maximum up to 7.5 mg daily is acceptable. However, in several randomised controlled trials, ivabradine can administered 5-10 mg twice daily [10]. Ivabradine reduce heart rate in patients who have HR >70 bpm and also incidence of coronary artery disease [11].

Surgery was not allowed to start till period of 10 minutes after intubation for the recording of baseline haemodynamic parameters. In the present study, after intubation all haemodynamic parameters of mean heart rate, SBP, DBP and MAP till period of 10 minutes were significantly less in oral ivabradine group as compared to the placebo group. Also, theses changes in haemodynamic parameters after extubation till period of 10 minutes were found to be significantly less in oral ivabradine group as compared to control group (p-value <0.005).

Ibrahim AN and Atallah RY observed that the haemodynamic parameters (heart rate, SBP, DBP and MAP) had mild changes after intubation and extubation compared to propranol group, in microlaryngoscopic surgeries [12]. A similar study by Mohamed MAL et al., concluded that both premedication with oral propranol (10 mg) and oral ivabradine (5 mg) in the evening before the day of surgery another 5 mg tablet one hour before anaesthesia induction was safe and effective in reducing reflex tachycardia that occurs during controlled nitroglycerine induced hypotensive anaesthesia in Functional Endoscopic Sinus Surgery (FESS). However, ivabradine compared to propranol was more effective with high safety margin in patients [13].

Kunwer R et al., also found that haemodynamic parameters during intubation and after 10 minutes of intubation were significantly lower in oral ivabradine group as compared to placebo group [14]. Similar to this study, haemodynamic parameters at extubation till period of 10 minutes also were stable compared to placebo group.

Similarly, Raghuram CG et al., found that oral ivabradine have reduced reflex tachycardia and haemodynamic parameters [15]. The authors compared the efficacy of oral ivabradine 5 mg at 6 p.m. on evening before the day of surgery and another 5 mg tablet one hour before intubation versus a placebo group. It was concluded that ivabradine is an excellent drug for preventing both increase in heart rate and, to a lesser extent blood pressure. Similar to this study, haemodynamic parameters at extubation till period of 10 minutes also were stable compared to placebo group. The fact of oral ivabradine have larger safety margin in view of reduced the heart rate without affecting haemodynamic instability [16].

The study concluded that ivabradine is simple, safe, cheap (Rs. 21.1 per tablet) and easy to use drug that gives adequate and satisfactory haemodynamic stability during induction, laryngoscopy, intubation and perioperative period. It also minimises the extent of high blood pressure seen during laryngoscopy and endotracheal intubation and help in return of blood pressure to the baseline values within a shorter period (around 3 min after endotracheal intubation) [17].

Limitation(s)

Compromised myocardium condition, clinically significant hypotension and bradycardia, uncontrolled diabetic mellitus, sick sinus syndrome, severe hepatic impairment, pacemaker dependency patients were not taken in this study.

CONCLUSION(S)

It is concluded that ivabradine is an useful drug to prevent abnormal rise in heart rate during laryngoscopy and intubation. It's stabilising effect of haemodynamic also extends up to extubation and immediate postoperative period. This study has shown no serious side-effects.

Acknowledgement

The authors extended their sincere thanks to Mr. Vasu Rathod statistician for his help and support in data collection and analysis.

REFERENCES

[1] Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. Br J Anaesth. 1987;59(3):295-99.
[2] Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect upon heart Surg Gynaec & Obst. 1940;70:157-62.
[3] Bruder N, Ortega D, Granthil C. Consequences and prevention methods of hemodynamic changes during laryngoscopy and intratracheal intubation. Ann Fr Anesth Reanim. 1992;11(1):57-71.
[4] De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Fail. 2008;10(6):550-55.
[5] Murat SN, Orcan S, Akdemir R, Dogan M, Kara E, Balci M, et al. Arrhythmic effects of ivabradine in patients with coronary artery disease. Clin Invest Med. 2009;32(5):E322-E326.
[6] Ripa C, Germano G, Caparra A, Capparuccia CA, Antonicelli R. Ivabradine use in refractory unstable angina: A case report. Int J Immunopathol Pharmacol. 2009;22(3):849-52.
[7] Borer JS, Tardif JC. Efficacy of ivabradine, a selective I (f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. Am J Cardiol. 2010;105(1):29-35.
[8] FDA Approves Corlanor to Treat Heart Failure. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ucm446899.htm.
[9] Yusuf S, Camm AJ. Sinus tachyarrhythmias and the specific bradycardic agents: A marriage made in heaven? J Cardiovasc Pharmacol Ther. 2003;8(2):89-05.
[10] Baruscotti M, Bucchi A, Difrancesco D. Physiology and pharmacology of the cardiac pacemaker ("funny") current. Pharmacol Ther, 2005;107(1):59-79.
[11] Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371(12):1091-99.
[12] Ibrahim AN, Atallah RY. Ivabradine versus propranolol given orally in microlaryngoscopic surgeries in attenuating stress response: A comparative prospective double blind randomised study. Egypt J Anaesth. 2016;32(4):503-11.
[13] Mohamed MAL, Hammad RA, Labib HA, Abdelgalial HA, Mohamed AM. Comparing the effect of oral ivabradine versus oral propranolol premedication during controlled hypotensive anaesthesia in functional endoscopic sinus surgery. Egyptian Journal of Anaesthesia. 2022;38:1572-79.
[14] Kunwer R, Joshi M, Pathak S. Prevention of haemodynamic changes during laryngoscopy and endotracheal intubation- a clinical study of oral ivabradine. International Journal of Contemporary Medical Research. 2016;3(7):1995-98.
[15] Raghuram CG, Singh DR, Kabra AV. Attenuation of haemodynamic response to laryngoscopy and endotracheal intubation using intra-oral ivabradine: A clinical study. J Evol Med Dent Sci. 2014;3(39):9944-55.
[16] Koruth JS, Lala A, Pinney S, Reddy VY, Dukkipati SR. The clinical use of ivabradine. J Am Coll Cardiol. 2017;70(14):1777-84.
[17] Arora V, Awasthi G, Singh RB, Singh V. Study of attenuation of hemodynamic response to laryngoscopy and endotracheal intubation using intra-oral ivabradine. Anaesthesia, Essays and Researches. 2019;13(1):138.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Anaesthesia, GCS Medical College, Hospital and Research Centre, Ahmedabad, Gujarat, India.
2. Professor, Department of Anaesthesia, GCS Medical College, Hospital and Research Centre, Ahmedabad, Gujarat, India.
3. Assistant Professor, Department of Anaesthesia, The Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India.
4. Professor, Department of Anaesthesia, Indira Gandhi Medical College and Research Institute, Puducherry, India.
5. Resident, Department of Anaesthesia, GCS Medical College, Hospital and Research Centre, Ahmedabad, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ankita Rushik Patel,
12, Tirthnagar Society Part-3, Bhuyangdev Cross Road, Ghatlodia,
Ahmedabad, Gujarat-380061, India.
E-mail: drankitapatel30@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 13, 2022
- Manual Googling: Nov 02, 2022
- iThenticate Software: Nov 05, 2022 (5%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Sep 02, 2022**
Date of Peer Review: **Sep 30, 2022**
Date of Acceptance: **Nov 06, 2022**
Date of Publishing: **Dec 01, 2022**