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

A. Jayanthi¹, B.K. Jayalakshmi², P.D. Subha³, O.K. Jayavel⁴

¹Assistant Professor, Department of Anaesthesia, Institute Of Obstetrics and Gynaecology, Madras Medical College, Chennai, Tamilnadu, India
²Associate Professor, Department of Anaesthesia, Government Kilpauk Medical College, Chennai, Tamilnadu, India
³Associate Professor, Department of Anaesthesia, Government Medical College, Vellore, India
⁴Assistant Professor, Department of Anaesthesia, Rsm Lying in Hospital, Stanley Medical College, Chennai, Tamilnadu, India

Abstract

Background: The role of anaesthesia and its level of safety in patients have gained prime importance. Therefore, the present study evaluates the effect of oral ivabradine on the hemodynamics during laryngoscopy and endotracheal intubation in patients undergoing surgical procedures under general anaesthesia.

Materials and Methods: This prospective randomised, single-blinded controlled study was conducted at Government Kilpack Medical College Hospital and Government Roya pettah Hospital, Chennai, between May 2021 and October 2021. Forty-six adult patients undergoing surgeries under general anaesthesia belonging to ASA PS 1 were selected. Total patients were divided into two groups as test (n=23, who received oral Ivabradine 5mg on a tablet at 6 pm on the evening before the day of surgery and one 5mg tablet one hour before intubation) and control group (n=23, tablet B complex one-hour intubation). Result: The mean age in years was 39.24± 9.290 (years) in group 1 and 60.82 ± 8.535 (years) in group 2. The mean weight in kilograms was 53.78±4.705 (Kg) in group 1 and 53.60 ± 3.580 (Kg) in group 2. There was no statistically significant difference between the two groups. The change in heart rate in group I and group II was statistically significant. Mean systolic blood pressure was raised during induction and returned to preoperative level within 3 minutes after intubation. Mean systolic pressures were within normal limits. There was no statistically significant difference between the two groups.

Conclusion: Ivabradine is an extremely useful drug to prevent an abnormal increase in HR seen during laryngoscopy and endotracheal intubation. Its proven safety enhances its claim for routine use in all patients at risk for hypertension during laryngoscopy and endotracheal intubation.

INTRODUCTION

In recent years, the role of anaesthesia and its level of safety in patients have gained prime importance. Stable hemodynamics has become the key to safe and successful induction and intubation. The usual response to laryngoscopy and endotracheal intubation is hypertension and tachycardia. They cause little consequence in healthy patients but may cause dangerous complications in patients with hypertension, raised intracranial pressure, aneurysmal vascular disease, and diseased cerebral vasculature or with ischemic heart disease [1]. Acute left ventricular failure, arrhythmias, intracranial haemorrhage, and pulmonary oedema might arise because of cardiovascular responses to laryngoscopy and intubation. Convulsions may be precipitated in eclamptic patients. Almost all dysrhythmias have been reported, including sinus tachycardia and bradycardia. 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 ischemic heart disease.[1-3]

There are many strategies used to blunt the intubation response. Endotracheal intubation is one of the most commonly performed procedures, where the role of anesthesiologists in patient care is noteworthy. Rapid and dramatic hemodynamic changes which adversely affect the patient may occur during laryngoscopy and intubation.[1-3]
Various strategies have been applied to attenuate these responses in high-risk individuals. These include topical and intravenous lignocaine, deep inhalational anaesthesia, ganglion blockers, regularisation, narcotics, adrenoceptor-blocking drugs, vasodilators, Nitroglycerine and Calcium channel blockers. Manipulations like minimizing the duration of laryngoscopy to less than 15 seconds, placing supraglottic devices like laryngeal mask airway (LMA), etc. Ivabradine is a cardiotonic agent. It is a highly selective inhibitor of funny current channel I (f). This channel inhibition diminishes the slope of spontaneous depolarization, leading to prolonging the time interval between consecutive action potentials in the SA node, thus decreasing the heart rate. This drug combines with the intracellular place of the ‘If’ channel and hinders it in a dose and voltage-dependent manner.[4,7] Thus, the present study evaluates the effect of oral ivabradine on the hemodynamics during laryngoscopy and endotracheal intubation in patients undergoing surgical procedures under general anaesthesia.

**MATERIALS AND METHODS**

This prospective randomised, single-blinded controlled study was conducted at Government Kilpack Medical College Hospital and Government Roya pattah Hospital, Chennai, between May 2021 and October 2021. Forty-six adult patients undergoing surgeries under general anaesthesia belonging to ASA PS 1 were selected.

All patients were assessed for inclusion and exclusion criteria and included in the study after obtaining written informed consent and were randomly allocated into two groups. Total patients were divided into two groups as follows:

**Test group:** Comprising of 23 patients who received oral Ivabradine 5mg on a tablet at 6 pm on the evening before the day of surgery and one 5mg tablet one hour before intubation.

**Control Group:** Comprising of 23 patients who received placebo tablet B complex one-hour intubation. These drugs were given by the anesthesiaiology residents who were not included in the study.

**Inclusion Criteria**

ASA PS1 patients (both sexes) who were posted for various procedures under general anaesthesia aged between 20-45 years old. Patients should have normal ECG and Mallam Patti grading I & II.

**Exclusion Criteria**

Patient refusal, presence of any medical disorder, presence of a history of any drug intake, patients with a history of chest pain/ palpitations/ syncope, history of respiratory problems, hepatic and Renal problems, patients belonging to ASA PS III and IV, patients with baseline heart rate less than 60 beats per minute and baseline systolic blood pressure less than 100mmhg, patients with ECG abnormalities, patients with difficult airway and intubation, and patients with a language barrier were excluded.

**Preoperative Preparation:** All patients satisfying inclusion criteria underwent the investigations, namely urine analysis, haemogram, blood chemistry, preoperative ECG, and X-Ray chest. On the day of surgery, patients who satisfied the inclusion criteria were selected. A preoperative evaluation was done, including a detailed history, clinical evaluation, and airway assessment.

Intravenous cannulation was done with an 18-gauge cannula after shifting the patient into the waiting area of the operation theatre and connected to a drip of ringer lactate. Premedication with an injection of Ondansetron 4mg slow I.V. given 20 minutes before induction. Inj. Glycopyrrolate 0.2mg I.V. was given 10 minutes before induction.

Continuous E.C.G., automated non-invasive blood pressure monitoring, and SpO2 monitoring were done. The premedication, induction agent, and muscle relaxant to facilitate intubation were standardized for both groups. During the preoxygenation, 100% Oxygen was given for 3 minutes, and during the induction, the patient was induced by Inj. Propofol 2 – 2.5 mg/kg body weight IV. Intubation was facilitated by using Inj. Succinyl Choline 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 minutes after the placebo in group 2.

Correlating with the peak action of the drug, intubation was achieved with an appropriate size oral cuffed Endotracheal tube with the aid of a 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 Inj. Atracurium 0.04 mg/kg top-up doses and Intermittent positive pressure ventilation with Nitrous Oxide and Oxygen in the ratio of 66, 33% using a circle absorber system connected to the Boyle’s machine. Surgery was not allowed to commence until the recordings were completed, around 10 minutes. Heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were recorded.

Ten minutes after intubation, after taking the recordings of hemodynamic parameters, Inj. Fentanyl 2mcg/kg I.V. and Inhalational agent sevoflurane were introduced into the anaesthetic technique along with using N2O + O2 + Atracurium by the closed circuit with the circle absorber. At the end of the surgery, neuromuscular blockade was reversed with Inj. Neostigmine 0.05mg/ kg and Inj. Glycopyrrolate 0.04mg/ kg I.V. All the patients were followed in the postoperative period. The comparing two groups looked for any incidence and adverse effect of Ivabradine in the postoperative period.

Data were analyzed using SPSS16.0V. Software. Two-sided independent student’s ‘t-tests to analyze continuous data and chi-square test for categorical data were used.
RESULTS

In our study, the blood pressure and mean heart rate of all patients in both groups were calculated and compared [Table 1]. The change in heart rate in group I and group II was statistically significant. The mean systolic blood pressure was raised during induction and returned to preoperative level within 3 minutes after intubation. Mean systolic pressures were within normal limits. There was statistically no significant difference between the two groups (p>0.05) [Table 2]. The mean age in years was 39.24± 9.290 (years) in group 1 and 60.82 ±8.535 (years) in group 2. There was no significant difference between the two groups. Of 46 patients, 18 were male, and 28 were female [Table 3]. The mean weight in kilograms was 53.78±4.705 (Kg) in group 1 and 53.60 ± 3.580 (Kg) in group 2. There was no significant difference between the two groups [Table 3].

| Variables | Group 1 | Group 2 |
|-----------|---------|---------|
| Age       | 22.91   | 24.09   |
| Weight    | 24.17   | 22.83   |
| Pre-op HR | 16.52   | 30.48   |
| IND/ HR   | 14.30   | 16.52   |
| 1 min HR  | 13.96   | 24.17   |
| 3 min HR  | 11.22   | 22.63   |
| 5 min HR  | 13.02   | 20.15   |
| 8 min HR  | 10.72   | 21.98   |
| 10 min HR | 25.59   | 20.48   |
| Pre-op SBP| 21.15   | 21.98   |
| IND/ SBP  | 16.33   | 20.63   |
| 1 min SBP | 17.74   | 20.15   |
| 5 min SBP | 18.33   | 20.54   |
| 8 min SBP | 21.98   | 20.48   |
| 10 min SBP| 26.43   | 26.35   |
| Pre-OP DBP| 26.15   | 26.85   |
| IND/ DBP  | 26.25   | 25.35   |
| 1 Min DBP | 26.95   | 25.02   |
| 3 Min DBP | 27.54   | 25.35   |
| 5 Min DBP | 26.85   | 25.02   |
| 8 Min DBP | 21.98   | 21.98   |
| 10 Min DBP| 26.43   | 26.35   |
| Pre-OP MAP| 26.07   | 26.85   |
| IND MAP   | 25.35   | 25.02   |
| 1 Min MAP | 25.02   | 25.35   |
| 3 Min MAP | 25.80   | 24.02   |
| 5 Min MAP | 24.02   | 23.46   |
| 8 Min MAP | 23.46   | 23.46   |
| 10 Min MAP| 24.54   | 24.54   |

DISCUSSION

In the present study, oral ivabradine was used to attenuate the haemodynamic responses to laryngoscopy, and endotracheal intubation and the same was compared with a placebo group. Blood pressure and heart rate response to laryngoscopy and intubation were studied in both groups who received the same drugs for induction and intubation. Our study showed no significant increase in the hemodynamic parameters in response to laryngoscopy and intubation in the test group compared to the control group. The minimal raise also returned to baseline immediately within a
minute. Whereas in the control group, the baseline reading was high, and the increase in the haemodynamic, especially the pulse rate, decreased to some extent and was significantly maintained above the normal value. 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 latter. They have suggested the use of β-blockers to attenuate responses.[8]

A study has shown that in coronary patients with a heart rate of 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) and coronary revascularization injuries (reperfusion injuries) by 30% (p=0.016).[9] In the shift study, ivabradine significantly reduced the risk of the primary composite endpoint of hospitalization for worsening heart failure or cardiovascular death by 18% (p<0.0001), undoubtedly causing a large increase in myocardial oxygen demand.[10]

Ivabradine has been very useful in controlling hemodynamics, particularly the heart rate in all patients. Especially in patients with contraindicated beta-blockers, such as asthmatics and diabetics. It is more useful in patients with diabetes and bronchial asthma, where beta blockers are either contraindicated or have limitations regarding their use. Even in difficult intubation where the intubation took a longer time (>20 seconds), ivabradine was extremely useful in quickly getting the heart rate back to baseline levels. This aspect is a definite advantage in patients whose hemodynamic responses may not be thoroughly blunted.[11-14] The drug, as seen from our study, can be used even in normotensive patients to prevent unwarranted and unwanted tachycardia commonly witnessed during general anaesthesia techniques. Ivabradine is an extremely simple, safe, economical, and easy-to-use drug for achieving satisfactory hemodynamic goals during anaesthesia, induction, and intubation.

CONCLUSION

We conclude that ivabradine is an extremely useful drug to prevent an abnormal increase in HR seen during laryngoscopy and endotracheal intubation. It also minimizes the extent of hypertension seen during laryngoscopy and endotracheal intubation. It helps return blood pressure to the baseline values within a short period (around 3 min after endotracheal intubation). It has proven safe in conditions such as ischemic heart disease, angina pectoris, diabetes mellitus, allergic bronchitis, and asthma, obstructive cardiomyopathies, enhancing its claim for routine use in all patients at risk for hypertension during laryngoscopy and endotracheal intubation.

REFERENCES

1. Alison J Smith, Neville W. Goodman. The hypertensive Groups PreOp. response to intubation. Do researchers acknowledge previous work? Can J Anaesth. 1997; 41:9-13
2. Elisabetha J Fox, Garry S, Constance H. Complications related to pressor response to endotracheal intubation. Anesthesiology. 1977; 47:524-525.
3. Bruder N, Ortega D. Granthall C. Consequences and prevention methods of haemodynamic changes during laryngoscopy and intratracheal intubation. Ann FrAnaesReanimation. 1992; 11:57-71.
4. De Ferrari GM, Muzzuero A. Agnesina L Bertolotti 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; 10:550-5.
5. Borer IS, Tardif JC. Efficacy of ivabradine, a selective I (f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. Am J Cardiol. 2010; 105:29-35.
6. Murat SN, Orcan S, Akdenir R, Dogan M, Kara E, Balci M. Arrhythmic effects of ivabradine in patients with coronary artery disease. Clin Invest Med 2009;32: E322-6.
7. Ripa C, Germano G, Caparra A, Capparuccia CA, Antonicelli R. Ivabradine use in refractory unstable angina: a case report. Int J Immunophath Pharmacol 2009; 22:849–52.
8. Kumar M SairiHaus, Vinita Singh. A study of cardiovascular response during laryngoscopy and intubation and their attenuation by ultrashort acting β - blocker esmolol. Indian J Anaesth. 2002; 46:104-106.
9. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:807–16.
10. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376:875–85.
11. Tchetchene, Philippe Gabriel Steg and Didier. Pharmacologic management of stable angina: role of ivabradine. European Heart Journal Supplements. 2006; 8:16–23
12. Liang M, Puri A, Devlin G. Heart rate and cardiovascular disease: an alternative to beta blockers. Cardiology. 2003; 100:149-55.
13. JC Tardif. Ivabradine: I (f) inhibition in the management of stable angina pectoris and other cardiovascular diseases. Drugs today. 2008; 44:171-81.
14. Saveleva I, Camen AJ. Novel I f current inhibitor ivabradine: safety considerations. Adv Cardiol. 2006; 43:79-96.