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STUDY OF ATTENUATION OF HEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION FOLLOWING ORAL IVABRADINE

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ABSTRACT **Background:** Laryngoscopy and intubation elicit significant hemodynamic alterations that have a negative impact on the patient's well-being during the perioperative phase. Diverse techniques have been used to mitigate the stress reaction in patients at a heightened risk. Ivabradine, a unique heart rate-lowering medication, is being investigated for its potential benefits in specific patient populations. **Aim:** To investigate the attenuation of hemodynamic response to laryngoscopy and endotracheal intubation following administration of oral Ivabradine. **Materials and Methods:** A randomized double blinded study was conducted in K.D. Medical College, Mathura, U.P. From July 2023 to January 2024.A total of 100 patients were allocated for the study and were evenly distributed into two groups using a computer-generated randomized table. In Group-A (test group), 50 patients were administered oral Ivabradine, a 5mg tablet, one hour before intubation. In Group-B (control group), 50 patients were given a placebo (sugar-coated tablet) one hour before intubation. **Results:** The mean heart rate in both groups were comparable at baseline, while during intubation and extubation, it was significantly less in group-A. Mean systolic blood pressure (SBP) in both groups were comparable at baseline, during intubation, post intubation period till 10 minutes, at extubation and post extubation till 10 minutes. Mean SBP was significantly less in group-A as compared to B. Mean diastolic blood pressure (DBP) in test and control group were comparable at baseline. At intubation, post intubation period till 10 minutes, at extubation and post extubation till 10 minutes. Mean DBP was significantly less in group-A as compared to B. Mean arterial pressure (MAP) in test and control group were comparable at baseline, while during intubation and extubation it was significantly less in group-A. There were no major side-effects of oral Ivabradine, but two patients had developed bradycardia and were managed adequately. **Conclusion:** Our findings indicate that Ivabradine is a straightforward, secure, cost-effective, and user-friendly medication that provides sufficient and appropriate hemodynamic stability during the perioperative phase. Additionally, it reduces the occurrence of elevated blood pressure seen during laryngoscopy and endotracheal intubation, facilitating a quicker return to baseline blood pressure levels.

KEYWORDS : Hemodynamic, Laryngoscopy, Endotracheal, Intubation, Oral Ivabradine

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 effects [1]. 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 artery disease, recent myocardial infarction, hypertension, geriatric population, pre-eclampsia, and stroke, 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 poor cardiovascular reserve with the resultant risk of myocardial infarction (MI), stroke, congestive heart failure or sudden death [3]. Ivabradine, is a highly selective inhibitor of "If" channels in the sinoatrial node (SA). 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 a sudden fall in blood pressure. 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 myocardial perfusion is reduced [4].

The α-2 receptors are located at multiple sites within both the peripheral and central nervous systems (CNS), as well as in visceral organs, including the liver, kidney, and pancreas. Additionally, they are found in the eyes, the media of blood vessel walls, and in platelets [5]. Classifying α-2 receptors based on their anatomical locations is challenging because they are found in presynaptic, postsynaptic, and extra synaptic sites. These receptors are categorized into three subtypes, each with distinct actions. [6]. 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 signaling 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[8,9].

MATERIALS AND METHODS

A randomized double blinded study was conducted in K.D. Medical College, Mathura, U.P. from July 2023 to January 2024. This study was conducted after obtaining approval from the Institutional Ethics Committee (approval number KDMCHRC/PG/IEC/2023/35). A total of 100 patients were enrolled in the study and randomly assigned to two equal groups using a computer-generated randomization table. All participants provided informed consent before participating. In Group-A (test group), 50 patients were administered oral Ivabradine, a 5mg tablet, one hour before intubation. In Group-B (control group), 50 patients were given a placebo (sugar-coated tablet) one hour before intubation

Inclusion Criteria

- ASA physical status I and II.
- Age group between 18-60 years of age of either sex.
- Mallampati grade I and II.
- Patients undergoing elective surgery under general anesthesia.

Exclusion Criteria

- Pregnancy

- Patients who did not provide consent
- Emergency surgery
- Anticipated difficult airway and difficult intubation

Methodology

Patients were given the tab ivabradine and sugar coated tablet one hour prior to induction as per their allotment. The procedures for induction, intubation, and maintenance of general anesthesia were identical for both 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 4mg 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 (2mg/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, 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 0.02mg/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. 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 (0.05mg/kg) and glycopyrrolate (0.008mg/kg). All the patients were thoroughly followed in the post-operative period. In the post-operative 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 beats per minute) was treated with injection Atropine 0.6mg intravenously stat and hypotension (BP <90/60mmHg) was treated with Mephentermine 6mg intravenously stat. The parameters that were recorded were, Heart rate, SBP, DBP and MAP. At the time of 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 and10 minutes after extubation.

RESULTS

The test and control groups were comparable regarding age, gender, weight, ASA grading, duration of surgery and time of medication, and intubation. SpO_2 and $EtCO_2$ were comparable in both groups. All the basic parameter was non-significant.

Table 1 Basic Parameter Of The Participants

Parameters	Group A	Group B	p-value
Age(in years)	48.52±6.85	45.05±6.58	0.14
Gender(Male/Female)	32: 18	35:15	0.29
Weight(kg)	66.17±3.89	65.63±3.96	0.37
ASA grading(I:II)	35:15	30:20	0.25
Duration of surgery	102.58±6.64	100.02±6.45	0.44

The mean heart rate in both groups were comparable at baseline, while during intubation and extubation it was significantly less in group A [Table2].

Table 2 Heart Rate of the Participants in Group A and Group B

Heart rate	Group A	Group B	p-value
Baseline	89.11±3.45	91.22±3.85	0.07
During intubation	91.25±3.44	105.14±4.25	<0.05
1 min	96.44±3.12	103.22±3.58	<0.05
3 min	93.74±2.69	107.85±2.99	<0.05
5 min	90.14±2.78	110.05±3.58	<0.05
8 min	85.08±3.33	112.25±3.88	<0.05
10 min	84.22±3.74	115.24±3.97	<0.05
At extubation	96.22±3.74	128.11±4.52	<0.05
1 min	94.24±3.22	118.24±4.62	<0.05
3 min	92.25±2.85	112.13±3.67	<0.05
5 min	90.04±2.66	111.32±3.74	<0.05
8 min	85.45±2.25	115.36±3.33	<0.05
10 min	84.24±1.74	110.77±2.85	<0.05

Mean SBP in both groups were comparable at baseline. At intubation, post intubation period till 10 minutes, at extubation and post extubation till 10 minutes, mean SBP was significantly less in group A as compared to B [Table 3].

Table 3. SBP in Group A and Group B

SBP	Group A	Group B	p-value
Baseline	119.85±4.52	128.36±3.96	0.11
During intubation	126.11±4.25	139.66±4.74	<0.05
1 min	127.85±4.85	139.98±4.15	<0.05
3 min	127.11±3.74	135.22±4.11	<0.05
5 min	125.24±2.55	133.63±3.96	<0.05
8 min	123.44±2.69	134.85±3.96	<0.05
10 min	120.55±2.69	135.29±3.74	<0.05
At extubation	122.25±3.74	138.85±5.22	<0.05
1 min	121.47±3.58	137.58±3.99	<0.05
3 min	121.47±2.94	134.77±3.55	<0.05
5 min	121.36±2.71	132.25±3.67	<0.05
8 min	120.47±2.67	132.21±3.84	<0.05
10 min	120.37±3.85	130.63±2.58	<0.05

Mean DBP in test and control group were comparable at baseline. At intubation, post intubation period till 10 minutes, at extubation and post extubation till 10 minutes, mean DBP was significantly less in group A as compared to B [Table 4].

Table 4. DBP in Group A and Group B

DBP	Group A	Group B	p-value
Baseline	77.25±2.85	84.25±3.14	0.22
During intubation	82.58±2.69	91.58±4.25	<0.05
1 min	77.96±2.74	87.55±4.64	<0.05
3 min	74.85±2.71	85.61±4.15	<0.05
5 min	76.55±2.41	86.14±3.17	<0.05
8 min	75.05±2.18	85.22±3.54	<0.05
10 min	74.21±2.32	87.69±3.74	<0.05
At extubation	80.25±3.63	90.52±4.84	<0.05
1 min	79.22±3.74	89.87±3.74	<0.05
3 min	78.25±3.71	88.54±3.61	<0.05
5 min	78.11±2.58	87.11±3.71	<0.05
8 min	78.01±2.56	85.52±4.52	<0.05
10 min	78.82±2.98	84.25±2.22	<0.05

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 5].

Table 5. Mean Arterial Pressure in Group A and Group B

Mean arterial pressure	Group A	Group B	p-value
Baseline	97.45±3.96	100.02±4.69	0.34
During intubation	93.33±3.74	105.88±5.85	<0.05
1 min	93.87±3.52	115.96±5.85	<0.05
3 min	94.89±3.63	119.25±5.63	<0.05
5 min	92.04±3.33	121.41±4.25	<0.05
8 min	91.21±3.11	123.11±5.22	<0.05
10 min	91.44±3.04	124.74±4.41	<0.05
At extubation	111.11±4.25	143.12±6.36	<0.05
1 min	110.25±4.12	136.88±4.63	<0.05
3 min	107.25±4.22	133.04±5.55	<0.05
5 min	106.89±3.66	127.88±4.61	<0.05
8 min	102.07±3.07	126.14±3.74	<0.05
10 min	97.99±2.98	122.24±3.74	<0.05

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

DISCUSSION

Reid and Brace first documented cardiac and hemodynamic alterations in 1940 while performing laryngoscopy and endotracheal intubation using traditional anesthetic methods. In anaesthetized patients, the sympathetic reaction, characterized by an elevation in heart rate and blood pressure, often reaches its maximum intensity between 30-45 seconds after laryngoscope and intubation. These temporary alterations may have severe and perhaps fatal consequences in individuals with cardiovascular and brain conditions [10].

Ivabradine received approval from the European Medicines Agency in 2005 and the United States Food and Drug Administration in the same

year. Nevertheless, ivabradine is specifically prescribed for managing symptoms of chronic stable angina pectoris in individuals with normal sinus rhythm who are unable to tolerate beta blockers. Additionally, it is being used off-label for the treatment of inappropriate sinus tachycardia [11]. The recommended initial oral dosage of ivabradine is 2.5 mg taken twice day, with a maximum daily dosage of 7.5 mg. Nevertheless, in many randomized controlled studies, ivabradine may be provided at a dosage of 5-10 mg twice day [12]. Ivabradine decreases heart rate in people with a heart rate greater than 70 beats per minute and also reduces the occurrence of coronary artery disease [13].

The surgery was prohibited from commencing until 10 minutes after intubation in order to capture the baseline hemodynamic data. In this research, it was shown that following intubation, the oral ivabradine group exhibited substantially lower hemodynamic parameters including mean heart rate, SBP, DBP, and MAP compared to the placebo group. These differences were seen for a duration of 10 minutes. The study observed that the changes in hemodynamic parameters following extubation for a period of 10 minutes were considerably lower in the oral ivabradine group compared to the control group (p-value <0.005).

Ibrahim AN and Atallah RY noted that the hemodynamic measures (heart rate, SBP, DBP, and MAP) exhibited slight variations during intubation and extubation, as opposed to the propranolol group, in microlaryngoscopic procedures in their study [14]. In a study conducted by Mohamed MAL et al., it was determined that administering oral propranolol (10 mg) and oral Ivabradine (5 mg) as premedication in the evening before surgery, followed by another 5 mg tablet one hour before anaesthesia induction, was both safe and effective in reducing reflex tachycardia during controlled nitroglycerine-induced hypotensive anesthesia in Functional Endoscopic Sinus Surgery (FESS). Nevertheless, ivabradine demonstrated greater efficacy and a higher level of safety compared to propranolol in individuals [15].

Kunwer R et al. discovered that the hemodynamic parameters during intubation and 10 minutes after intubation were notably reduced in the oral ivabradine group compared to the placebo group [16]. Similar to this research, the hemodynamic parameters were steady throughout the extubation interval and up to 10 minutes, in comparison to the placebo group.

In a similar vein, Raghuram CG et al. discovered that oral administration of ivabradine effectively decreased reflex tachycardia and improved hemodynamic parameters [17]. The researchers conducted a study to assess the effectiveness of oral ivabradine 5 mg taken at 6 p.m. on the evening before operation, followed by another 5 mg pill one hour before intubation, with a group that received a placebo. It determined that ivabradine is a very effective medication for avoiding both elevated heart rate and, to a lesser degree, high blood pressure. Similar to this research, the hemodynamic parameters were steady throughout the extubation interval and up to 10 minutes, in comparison to the placebo group. Oral administration of ivabradine is advantageous due to its wider safety margin, since it reduces heart rate without causing any negative impact on hemodynamic stability [18].

CONCLUSION

Our findings indicate that ivabradine is a straightforward, secure, cost-effective, and user-friendly medication that provides sufficient and appropriate hemodynamic stability during the process of induction, laryngoscopy, intubation, and the postoperative phase. Additionally, it reduces the occurrence of elevated blood pressure seen during laryngoscopy and endotracheal intubation, facilitating a quicker return to baseline blood pressure levels.

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):295-9. doi: 10.1093/bja/59.3.295, PMID 3828177.
2. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex upon head. Surg Gynecol Obstet. 1940; 70:157-62.
3. Hagberg CA, Artime CA. Airway management in adults: Miller's anesthesia. Miller RD: Cohen NH, Erikson LI, Fleisher LA, Wiener-Kronish JP, Young WL. 8 th Ed.; 2015, 1:1647-1680.
4. Murat SN, Orcan S, Akdemir R, Dogan M, Kara E, Balci M. Arrhythmic effects of ivabradine in patients with coronary artery disease. Clin Invest Med. 2009; 32(5):E322-6. doi: 10.25011/cim.v32i5.6919, PMID 19796572.
5. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists. Anesthesiology. 1991; 74(3):581-605. doi: 10.1097/00000542-199103000-00029.
6. Patel, A. R., Chhanwal, H. S., Solanki, R. N., Natarajan, P., & Kacha, N. (2022). Consequence and prevention of haemodynamic stress response during laryngoscopy and endotracheal intubation with oral Ivabradine: A multicentric randomized controlled study. Journal of Clinical and Diagnostic Research, 16(12), UC06-UC09.
7. Arora, V., Awasthi, G., Singh, R. B., & Singh, V. (2019). Study of attenuation of hemodynamic response to laryngoscopy and endotracheal intubation using intra-oral ivabradine. Anesthesia Essays and Researches, 13(1), 138-143. https://doi.org/10.4103/aer.AER_175_18
8. Kunwer, R., Joshi, M., & Pathak, S. (2016). Prevention of hemodynamic changes during laryngoscopy and endotracheal intubation- a clinical study of oral ivabradine. International Journal of Contemporary Medical Research, 3(7), 1995-1998.
9. Gosavi, R., Alam, K. R., Ghongate, G., & Phalgune, D. (2021). A Comparative Study to Assess the Effect of Oral Gabapentin Vs Oral Clonidine in Attenuating Haemodynamic Response of the Patients Undergoing Laryngoscopy and Tracheal Intubation. Asian Journal of Pharmaceutical and Health Sciences, 11(2), 2449-2456. https://doi.org/10.5530/ajphs.2021.11.6
10. Reid, L. C., & Brace, D. E. (1940). Irritation of the respiratory tract and its reflex effect upon heart. Surgery, Gynecology & Obstetrics, 70, 157-162.
11. Yusuf, S., & Camm, A. J. (2003). Sinus tachyarrhythmias and the specific bradycardic agents: A marriage made in heaven? Journal of Cardiovascular Pharmacology and Therapeutics, 8(2), 89-105. https://doi.org/10.1177/107424840300800202
12. Baruscotti, M., Bucchi, A., & Difrancesco, D. (2005). Physiology and pharmacology of the cardiac pacemaker ('funny') current. Pharmacology & Therapeutics, 107(1), 59-79. https://doi.org/10.1016/j.pharmthera.2005.01.005
13. Fox, K., Ford, I., Steg, P. G., Tardif, J. C., Tendera, M., Ferrari, R., & Bhatt, D. L. (2014). Ivabradine in stable coronary artery disease without clinical heart failure. New England Journal of Medicine, 371(12), 1091-1099. https://doi.org/10.1056/NEJMoa1406430
14. Ibrahim, A. N., & Atallah, R. Y. (2016). Ivabradine versus propranolol given orally in microlaryngoscopic surgeries in attenuating stress response: A comparative prospective double-blind randomized study. Egyptian Journal of Anesthesia, 32(4), 503-511. https://doi.org/10.1016/j.egja.2016.08.020
15. Mohamed, M. A. L., Hammad, R. A., Labib, H. A., Abdelgalial, H. A., & Mohamed, A. M. (2022). Comparing the effect of oral ivabradine versus oral propranolol premedication during controlled hypotensive anesthesia in functional endoscopic sinus surgery. Egyptian Journal of Anesthesia, 38, 1572-1579.
16. Kunwer, R., Joshi, M., & Pathak, S. (2016). Prevention of hemodynamic changes during laryngoscopy and endotracheal intubation: A clinical study of oral ivabradine. International Journal of Contemporary Medical Research, 3(7), 1995-1998.
17. R, C. G., Singh, D. R., & Kabra, A. V. (2014). Attenuation of hemodynamic response to laryngoscopy and endotracheal intubation using intra-oral ivabradine: A clinical study. Journal of Evolution of Medical and Dental Sciences, 3(39), 9944-9955. https://doi.org/10.14260/jemds/2014/3289
18. Koruth, J. S., Lala, A., Pinney, S., Reddy, V. Y., & Dukkipati, S. R. (2017). The clinical use of ivabradine. Journal of the American College of Cardiology, 70(14), 1777-1784. https://doi.org/10.1016/j.jacc.2017.08.038