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# Study on Oral Nebivolol in Attenuating the Cardio Vascular Responses to Laryngoscopy and Endotracheal Intubation

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**Abstract**

*Introduction:* Laryngoscopy and intubation are almost always associated with hemodynamic changes due to sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. *Aim:* To study the efficacy of oral Nebivolol in attenuating the cardio vascular reflex responses to laryngoscopy and endotracheal intubation. *Materials and methods:* The attenuation of cardiovascular reflex responses to laryngoscopy and endotracheal intubation has been done with oral nebivolol, a long acting beta-1 blocker in 25 healthy ASA grades 1 patients of both sexes b/w age groups 25-60 yrs. and compares with 25 others in the same age group, termed as control. The study group receives oral nebivolol 5 mg once daily for those below 50 kgs. In the premedication inj. Glycopyrolate 0.2 mg IM and inj. Ketorolac 1 mg/kg IM was given in both groups, inj. Glycopylate was preffered over injection atropine as it has better antisecretory properties with minimal cardiac effects, which would change basic monitoring values. *Results:* Laryngoscopy and endotracheal intubation there was significant increase in blood pressure (SAP, DAP and MPA) and heart rate in the control group, but was significantly less in the study who received the beta blocker nebivolol. In control group rate pressure product, a measure of myocardial oxygen demand was increased significant after laryngoscopy and endotracheal intubation. *Conclusion:* Hence, because of long duration of action and being beta, selective agent, oral nebivolol agent when used prior to surgery ensures a stable normotensive or a mild hypotensive field during surgery.

**Keywords:** Nebivolol; Laryngoscopy; Endotracheal Intubation.

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## Introduction

Endotracheal intubation is translaryngeal placement of endotracheal tube into trachea via, the nose or mouth. It was during the world war-I that blind naos-tracheal intubation was popularized by rowbotham and Magill. Continued improvement in equipment and use of neuromuscular blockers combined with technical skills of anesthesiologist have made endotracheal intubation safe in common practice in modern day anesthesia. Commonly observed cardiovascular effects seen during intubation arehypertension and tachycardia which have been recognized since.

Direct recording of sympathetic nervous activity is difficult in man, but measurement of plasma

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catecholamine has demonstrated increase in noradrenaline following laryngoscopy.

Attempts were made to differentiate between the effects of laryngoscopy and those of tracheal intubation and their individual contribution to hemodynamic changes. Prys Roberts et al. [1] observed that a majority of patients had reflex tachycardia and hypertension well before the act of intubation and this was often enhanced by intubation. So, it is laryngoscopy rather than endotracheal intubation, which generates the stimulus.Increase in heart rate and blood pressure is transitory, variable and unpredictable. the CVS response to intubation is exaggerated in hypertensive patients.

Cardiovascular response to intubation is of a serious concern in patients with hypertension, raised intracranial pressure, diseased cerebral vasculature or with ischemic heart disease where increase in myocardial oxygen consumption can lead to myocardial infraction [2,3]. Cardiovascular effects are observed during induction, during and after intubation during recovery of the patient. The various complications observed during endotracheal intubation are arrhythmias, myocardial ischemia, acute left ventricular failure, intracranial hemorrhage and pulmonary edema. Convulsions may be precipitated in eclamptic patients. Almost all types of dysrhythmias have been reported in addition to sinus tachycardia. The common abnormalities are nodal rhythm, atrial and ventricular extra systoles and pulses alternans. Less commonly, multifocal extrasystoles, pulsus bigeminus and atrial fibrillation have been reported. Heart block, ventricular tachycardia and fibrillation are fortunately rare. Radionuclide studies have shown that stress response to laryngoscopy and endotracheal intubation produce a rapid decline in global left ventricular function (ejection fraction) within seconds, often exercise in patients with symptomatic artery disease. Therefore, various techniques have been used to attenuate these responses. there are local, central and peripheral methods to achieve this purpose.Theseinclude topical and intravenous lignocaine, deep inhalational anesthetics, ganglion blockers, precurarization, narcotics (morphine, buprenorphine fentanyl, alfentanyl) adrenoceptor blocking drugs, vasodilators, nitroglycerin ointment, intranasal nitroglycerin, calcium channel blockers, reducing the duration of direct laryngoscopy to less than 15 seconds and avoiding laryngoscopy and resorting to blind nasal intubation.

Present study is undertaken to evaluate the efficacy of a new beta blocker viz., oral Nebivolol, a novel long acting beta blocker with endothelial protection activity, to attenuate cardiovascular Reponses to laryngoscopy and endotracheal intubation in health, ASA grade I normotensive patients.

**Material and Methods**

Fifty healthy ASA grades 1 patients scheduled for elective general surgery were selected forth present study Patients in group of 25 yrs. to 60 yrs. of either sex were selected and their weight, age and sex were comparable in both the groups. These fifty patients divided into two groups, control group consisting of 25 patients and study group consisting of 25 patients.

Complete paranesthesia checkup was done 3-4 days prior to surgery, detailed history taken and complete physical examination performed and presence of any organic medical disorder and history of other drug intake was excluded. Patients with history of angina, asthma, other respiratory disorders like COPD, atelectasis, pneumothorax, tuberculosis, haemothorax, pneumothorax were excluded from the study. patients with raised intracranial pressure were also excluded.

Patients with ECG changes of coronary artery disease, cardiac conducting defects, left ventricular hypertrophy, bradycardia (HR<60) congestive cardiac failure, cardiac valvular abnormalities myocardial disease another congenital cardiac defect were also excluded.

Laboratory Investigations: the laboratory investigation performed included a haemogram, serum creatinine, blood sugar, ECG and chest X-ray. Patients in study group were started 3-4 days prior to surgery with tab. nebivolol (nubeta) 5 mg/day orally for those weight was below fifty kilograms (50 kgs). Those patients, whose weight was greater than fifty kilograms (>50 kgs) were given tab nebivol (nublet) 10 mg/day. The drug was allowed to be taken at 8:00 AM every morning beginning 3-4 days prior to surgery. The last dose of nebivolol was given to the patients 4-6 hrs prior to induction of anesthesia with sip of water (upto ½ glass of water).

The drugs used to premedication and muscle relaxation to facilitate intubation were standardized for two groups (study and control). Boyled machine and circuits were thoroughly checked and required size endotracheal tubes and a Macintosh curved blade laryngoscope with required sized blades was kept. Before induction of anesthesia, patients

pulse rate, blood pressure and ECG monitoring started. This was done by monitoring with ECG in the standard limb leads along with SP02 maintaining. An adult sphynomanometer cuff tied to the left arm and attached to non-invasions blood pressure monitor.

Premedication: premedication was given with glycopyrrolate 0.2 mg and ketocele 1 mg/kg body weight intramuscularly 60 minutes before induction.

Induction: induction was done with thropentone sodium, dose of 5 mg/kg.

Intubation: intubation was performed with vecornium bromide with a dose of 0.1 mg/kg muscle relaxant used was vecuronium bromide for maintenance of anesthesia.

Patients requiring intubation time more than 40 seconds were excluded from the study. Halothane was used in maintenance of anesthesia only 15 minutes after induction prevent wrong interpretation. at the end of surgery, the residual neuromuscular was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Systolic blood pressure, diastolic blood pressure and heart rate were recorded at regular intervals in both control and study group as follows.

Just before induction, after induction at 1st, 2nd, 3rd, 4th, 5th, 10th and 15th minutes.

## Results

The characteristics of patients are shown in the following anthropometric

**Table 1:** Demographic details in both groups.

| Demographic details | Control(n=25) Mean(SD) | Study(n=25) Mean(SD) |
|---|---|---|
| Age in Yrs | 36.68(8.09) | 40(10.35) |
| Range | 28-44 | 30-40 |
| Weight(kgs) | 50.00(11.31) | 51.56(5.59) |
| Range | 43-60 | 40-58 |
| Male/female(nos) | 14/11 | 16/9 |
| Range | 26-56 | 25-60 |

There is no significant difference of demographic parameters in both groups.

**Table 2:** Hemodynamic reading recorded at the time of pre-anesthetic checkup.

| Pre-anesthetic checkup | Control group n=25 Mean(SD) | Study group n=25 Mean(SD) | P-Value |
|---|---|---|---|
| SPD (mm Hg) | 119.6(12.74) | 127.44(15.88) | p>0.05 |
| DAP (mm Hg) | 76(7.64) | 78.8(11.58) | p>0.05 |
| MAP (mm hg) | 99.23(6.31) | 100.2(7.01) | p>0.05 |
| heart rate (beat / minute) | 88.32(9.86) | 91.6(9.02) | p>0.05 |

Hemodynamic reading recorded at the time of pre-anesthetic checkup are shown above in the table are heart rate, systolic arterial pressure (SAP) diastolic arterial pressure (DAP) are almost similar in both control and study groups and there are no significant differences at the time of pre-anesthetic checkup.

In control group also standardized with same pre-medication the value taken as pre-induction values (basalvalues) in study and control group. Hemodynamic readings heart rate, systolic arterial pressure (sap), diastolic arterial pressure (DAP) are amount similar in both (control with study) group and there is insignificant difference at the time of pre-anestheticcheckup.

Following induction, there is fall in systolic, diastolic and mean arterial pressures in both groups compared to theirpre-inductionvalue (basal values) respectively the fall is significantly statistically in the same group and between the two groups ($p<0.05$). more significant in MAP and heart rate (HR). There is rise in the heart rate in both groups

**Table 3:** Hemodynamic values recorded at the time of induction (pre-induction)

| Pre-induction | Control group n=25 Mean(SD) | Study group n=25 Mean(SD) | P-Value |
|---|---|---|---|
| SPD (mm Hg) | 121.68(11.44) | 113.2(16.66) | P<0.005 significant |
| DAP (mm Hg) | 77.92(6.56) | 70.2(11) | p>0.10 |
| MAP (mm hg) | 92.51(7.26) | 85.2(8.86) | P<0.001 significant |
| heart rate (beat / minute) | 91.28(9.79) | 78.12(7.79) | P<0.001 significant |
| Rate pressure product (RPP) | 11048.64 | 10900.40 | p>0.10 |
| *After induction* | | | |
| SAP (mm hg) | 119.52(20.53) | 101.16(14.40) | P<0.005 significant |
| DAP (mm hg) | 79.72(8.6) | 68.12(11.95) | P<0.05 significant |
| MAP (mm hg) | 90.70(6.00) | 80.00(9.40) | P<0.001 significant |
| Heart rate (beat/mt) | 105.08(11.88) | 86.96(8.62) | P<0.001 significant |
| Rate pressure product | 12670.12 | 9267.60 | P<0.001 significant |

**Table 4:** Hemodynamic responses to laryngo scopy and endotracheal intubation

| Cardio Vascular parameters | 1 minutes after laryngoscopy and intubation | 2 minutes after laryngoscopy | 3 minutes after laryngoscopy | 4 minutes after laryngoscopy | 5 minutes after laryngoscopy | 10 minutes after laryngoscopy | 15 minutes after laryngoscopy |
|---|---|---|---|---|---|---|---|
| SAP in mmHgs | 152.4 (12.34)<br>129.6 (15.67) | 150.96 (13.57)<br>115.8 (15.52) | 149.56 (13.25)<br>111.52 (14.93) | 147.04 (15.13)<br>110 (16.33) | 146.4 (15.53)<br>109.6 (16.20) | 142.72 (10.70)<br>109.2 (14.70) | 139.68 (19.34)<br>106.80 (14.06) |
| DAP in mmHgs | 88.88 (7.21)<br>81.48 (9.67) | 86.64 (7.20)<br>78.80 (9.19) | 85.60 (7.37)<br>74.16 (10.13) | 83.60 (7.37)<br>72.96 (10) | 81.44 (7.06)<br>72.96 (10) | 81.84 (6.40)<br>71.36 (7.83) | 81.44 (6.15)<br>70.64 (8.85) |
| MAP in mmHgs | 110.00 (7.05)<br>98.16 (8.90) | 106.08 (8.62)<br>91.03 (6.92) | 104.29 (6.97)<br>84.51 (8.35) | 102.75 (5.80)<br>86.33 (8.92) | 105.33 (8.67)<br>85.17 (5.08) | 115.26 (10.40)<br>95.36 (6.82) | 100.58 (12.23)<br>86.93 (7.96) |
| Heart rate beat/minutes | 121.92 (6.28)<br>99.8 (5.92) | 121.6 (5.26)<br>86.88 (5.39) | 120.36 (4.54)<br>79.6 (8.30) | 119.2 (5.42)<br>76.64 (5.71) | 118.52 (4.20)<br>76.32 (5.82) | 118.04 (4.42)<br>75.4 (4.55) | 117.36 (4.35)<br>73.84 (4.2) |
| Rate pressure product | 18492.00<br>11990.82 | 18356.73<br>11896.63 | 17920.64<br>887640 | 17467.67<br>8754.00 | 17128.00<br>8236.27 | 16893.67<br>8233.68 | 16382.84<br>7896.11 |

SAP- Systolic arterial pressure, DAP-Diastolic arterial pressure, MAP-Mean arterial pressure

HR- Heart rate, RPP=Rate pressure product

after induction this also significant ($p<0.001$) statistically.

In the control group the hemodynamic values increased very much above the basal values.

Systolic arterial pressure -30.72

Diastolic arterial pressure -10.96 mmHg

Mean arterial pressure -17.49 mmHg

Heart rate -30.64/beat/min

In the study group the difference is as follows:

Systolic arterial pressure -18.4 mmHg

Diastolic arterial pressure -9.28 mm Hg

Mean arterial pressure -12.96 mmHg

Heart rate -23.68 beats/minutes

This comparison gross increase in the hemodynamic responses to pre-induction readings (basal values) they are significant statistically.

Difference b/w the two groups (control and study) i.e., systolic arterial blood pressure ($p<0.001$), diastolic arterial pressure ($p<0.001$), mean arterial blood pressure ($p<0.001$) and heart rate ($p<0.001$) are statistically significant. There is also profound difference in rate pressure product values b/w control and study group.

There is not much difference b/w pre-induction value and 3 minutes after intubation. It shows attenuation response was achieved by 3rd minutes in study group, whereas in control group there is significant difference seen b/w pre-induction and there minutes and three after intubation values statistically.

The values 4 mints after intubation shows there is not much difference b/w control and study group compare three minutes after intubation values. Surgical incision was given five minutes after post intubation reading was recorded. All the patients were stable hemodynamically during the intra operative period and post-operative period; there was no incidence of bradycardia or hypertension during the study.

The values taken 10 min, 15 min, after intubation in respective tables both in control and study group without supplementing any drug. In control group the values did not touch the base line even by fifteenth minute after intubation. Whereas in study the values touched to base line by the 15th minute. This study shows nebivol was useful in attenuating the introduction response. At the end of surgery all the patients were reversed with neostigmine methyl sulphate and atropine sulphate. All the patients were followed in the post-operative period. There were no incidence of nauseas, vomiting, bradycardia, hypotension or any other untoward side effects.

## Discussion

Reflex cardiovascular effects of laryngoscopy and endotracheal intubation in anaesthetized patients have been described previously and included a pressor response and tachycardia which occur at their peak approximately 30 minutes 45 seconds and the peak sustained till 1 minute after laryngoscopy and intubation [4].

There have been many studies which demonstrated increased sympathetic response to laryngoscopy and endotracheal intubations there changes during laryngoscopy and endotracheal intubation can lead to major complication like left ventricular failure, acute myocardial infarction, intracerebral hemorrhage In hypertensive patients this hyper dynamic response causes large increase

in myocardial oxygen demand Attempts to attenuate have responses by various drugs and techniques have met with varied success [5].

Various B. blockers have been used to attenuate the cardiovascular response to laryngoscopy and intubation with variable to reasonable amount of success [6]. In the present study oral nebovol a long acting beta-1 blockers (B1) 5 mg once daily started 3-4 days prior to surgery orally was usedto study its efficacy in the attenuation of pressor response to laryngoscopy and intubation. This study was conducted in normotensive, ASA grade -1 patents belonging to the age group 25-60 yrs, undergoing elective surgery.

The study consisted of 25 patients taken as control group and 25 patients taken as study group, who received tablet nebivolol 5 mg once orally and started 3-4 days prior to surgery. Both groups were pre-medicated with injection hetorlac 1 mg/kg weight I.M and glycopyrolate 0.2 mg IM 60-90 minutes before surgery. Blood pressure and heart rate response to laryngoscopy and intubation was studied in both groups who received the same drugs for induction and intubation. There was statistically no significant difference between the pre-inductionvalues of systolic diastolic arterial pressure sin both groups, but there is significant difference in mean arterial pressure and heart, rate statistically ($p<0.001$). mean arterial pressure, heart rate and rate pressure product ratios are lower in the study group who received tablet nebivolol.

After induction with thiopentone and vecuronium bromide difference in hemodynamic value b/w two groups was significant statistically in all the parameters, there was much fall in systolic arterial pressure and increase in heart rate to pre-induction values. One minute after laryngoscopy and intubation there was significant difference statistically in the hemodynamic values b/w the two groups ($p<0.001$). The increase in hemodynamic values till the 5$^{th}$ minute after intubation to pre-induction values in control group was significant statistically ($p<0.001$). so, this study confirms the potential hypertensive and tachycardia effects of laryngoscopy and intubation.

In the study group increase inhemodynamic values occurred till 2 minutes after intubation and almost touched the preinduction values (basal values) by 3$^{rd}$ minute change of hemodynamic values statistically only 1$^{st}$ one mte after intubation ($p<0.001$). In hemodynamic value the increase in study group compared to prelinduction values in two or 3 minutes intubation was not significant statistically. In the study group the difference observed at 3 minutes after laryngoscopy and endotracheal intubation to prenduction values as Heart rate 3.48 beats/minutes, Systolic arterial pressure as 0.32 mm Hg, Diastolic arterial pressure as 1.96 mm Hg, Mean arterial pressure as 69 mm Hg and Rate pressure product is also within the critical level (< 12,000). The changes in study group when compares to the changes in control group were statistically significant ($p<0.001$). this shows that oral nebivolol effectively attenuates the hemodynamic response to laryngoscopy and endotracheal intubation [7].

In the study groups the systolic, diastolic, mean arterial and heart rate have returned to the basal values, whereas in the control group the hemodynamic values are still above their basal values, whereas in the control group the hemodynamic values are still above their basal values and arte statistically significant ($p<0.001$) rate pressure product which denotes myocardial oxygen consumption was increased very much above the critical level 12,00 in the control groups after laryngoscopy and intubation but not in the study groups. The hemodynamic values in control group did not touch the basal values till 5 minutes after laryngoscopy and intubation the values are significant statistically ($p<0.001$). In the study group the hemodynamic values are similar to their values respectively which is not significant statistically at 5 mats after laryngoscopy and intubation.

There are not many studies on the effects of nebivolol a long acting B1 blocker on the attenuation of hemodynamic presser responses 6to laryngoscopy and intubation. Studies have been done on other B blockers i.e., atenolol, practolol, metoprolol, pindolol, esmolol, labettclol etc., The present study with nebivolol a new long acting beta blocker has given a positive result i.e., a good response of attenuation of hemodynamic responses to laryngoscopy and endotracheal intubation [8].

Study group patients were given Nebivolol (nubeta) orally 5 mg/day three (3) days before the surgery and on the day of surgery morning fourth day (4) at 5 AM with a sip of water and the patients were premediated with inj. Glycopyrrolate) 0.2 mg+inj. Ketorlac 1 mg/kg body weight IM and the hemodynamic value recorded. Significant changes of hemodynamic values were in study group.

## Conclusion

The principal advantages observed with nebivolol during the study are Good attenuation of heart rate response, Good attenuation of blood response.

There was good intra operative protection against cardiovascular responses to surgical stimulation. There was good response to the pressor effects during extubating in most of the cases because of its long half-life. The during is easily available, easy to administer, cost is reasonable and needs to be administered only one a day. It has minimal side effects. No side effects were observed during the study.

It is concluded that enhanced sympathetic drive which results in hypertension and increased heart rate, associated with laryngoscopy and endotracheal intubation was attenuated with use of long acting beta-1 selective blocker tab. Nebivolol. The rate pressure product which is a major determinant of myocardial oxygen demand was also decreased because of the nebivolol.

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