Original Article

Comparison of the Effects of Nitroglycerin, Labetalol and Lidocaine in Hypertensive Patients in Attenuation of the Endotracheal Intubation Reflex

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ABSTRACT

Background: *Laryngoscopy and tracheal intubation integral parts of general anesthesia which may cause acute haemodynamic instability. Hypertensive patients are more prone of developing cardiovascular complications such as pulmonary oedema, cardiac failure and cerebrovascular haemorrhage. To attenuate such intubation reflex, some drugs are used, e.g., opioids. lidocaine sodium nitroprusside, nitroglycerin, beta blockers, calcium channel blockers etc.*

Objective: *The purpose of the study is to see the effectiveness of nitroglycerin, labetalol and lidocaine in attenuation of intubation reflex and their anesthetic outcome in hypertensive patients.*

Methods: *This randomized controlled study was carried out in the Department of Anesthesia, Pain, Palliative and Intensive care Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between March and September of 2021. A total of 90 patients were included: 30 in each group as per inclusion and exclusion criteria. Group A patients received inj. nitroglycerin 2 minutes before intubation, while group B patients received inj. labetalol 0.25mg/kg 5 minutes before intubation, and group C was given 2% lidocaine 1.5mg/kg 2 minutes before intubation. Haemodynamic status of all patients was checked before and after intubation.*

Results: *Mean age of the patients was 44.4±10.9 years in group A, 47.6±9.4 years in group B and 46.4±10.6 years in group C. Heart rate after intubation was low and statistically significant in groups-B after 1.2 and 5 minutes. Regarding mean arterial pressure (MAP), group A patients had significantly low blood pressure. Rate pressure product (RRP) of the patients was significantly low in group B at 1 minute, 2 minutes and 5 minutes. Regarding ECG changes sinus tachycardia was observed in 26.6%, 86.6% and 20% in group A, group B and group C immediately after intubation. Groups B patients showed lower incidence of sinus tachycardia than that of two other groups and showed no premature ventricular contractions, whereas group A (6.7%) and group C (3.3%) showed premature ventricular contractions.*

Conclusion: *Labetalol showed better rhythm control, mean arterial pressure and less incidence of tachycardia. To summarize, labetalol is safer and more effective than nitroglycerin and lidocaine to attenuate the endotracheal intubation reflex in hypertensive patients.*

Keywords: *Endotracheal intubation reflex, hypertensive patient, nitroglycerin, labetalol, lidocaine*

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INTRODUCTION

Tracheal intubation is an important part of general anaesthesia where muscle relaxation and controlled ventilation is needed. The most important response of laryngoscopy and intubation often results in hypertension and tachycardia.[1,2] These responses are mediated by the cardioaccelerator nerves and sympathetic chain ganglia with widespread release of norepinephrine and epinephrine.[2] The degree of reflex response to laryngeal stimulation appears to vary with the depth of anaesthesia, the duration as well as on patient-dependent variables including age and cardiovascular disease.[3] These effects are generally well tolerated by overall healthy patients but can be lethal to patients with preexisting conditions such as hypertension, coronary artery disease, recent myocardial infarction, geriatric population, pre- eclampsia, and cerebrovascular pathology such as tumours, aneurysms or increased intracranial pressure etc. and are at increased risk of morbidity and mortality.[4]

Hypertension is a common comorbid condition among Bangladeshi adults which is increasing every year.[5] During laryngoscopy and endotracheal intubation hypertensive patients more frequently develop various cardiovascular events such as pulmonary oedema, cardiac failure, and cerebrovascular haemorrhage than that of normotensive patients.[6] Endotracheal intubation induces increased plasma concentration of catecholamines and there may be associated myocardial ischaemia and cerebral haemorrhage. There have been various attempts were taken to attenuate this sudden response. However, no specific regimen or drug combination has demonstrated effectiveness in the attenuation of this response in patients requiring endotracheal intubation.[6,7] Methods like smooth and gentle intubation, blocking the glossopharyngeal nerve and superior laryngeal nerve have been used but none of these approaches have been proved entirely satisfactory.[6] Increasing the depth of anaesthesia often results in haemodynamic compromise. A wide variety of pharmacological agents were also tried to attenuate the hemodynamic responses to laryngoscopy and endotracheal intubation like lidocaine, opioids, sodium nitroprusside, nitroglycerin, beta blockers, calcium channel blockers with varying results.[7]

Nitroglycerin, a direct acting vascular smooth muscle relaxant intravenous or sublingually has been used for attenuating hypertensive response during laryngoscopy, tracheal intubation and for controlling hypertension during intubation.[8] Nitroglycerin generates nitric oxide in vascular smooth muscle which produces vasodilation leading to decrease in blood pressure; however, it increases blood flow to the myocardium.[9] Intravenous bolus dose of nitroglycerin as 1-2 ìg/kg administered at the start of laryngoscopy and intubation was found to be effective in attenuating the hypertensive response.[8]

Labetalol is an antihypertensive drug which is selective alpha-1 and nonselective beta-1 and beta-2 adrenergic antagonist. It decreases the systemic vascular resistance by alpha-1 blockade and thereby lowers the blood pressure. It also causes simultaneous beta blockade which attenuates the reflex tachycardia occurring because of vasodilatation.[10,11] It was found that inj. labetalol as administered 0.15-0.3 mg/kg body weight has effectively attenuates the sympathoadrenal response to laryngoscopy and intubation.[11]

Lidocaine was used initially in the management of arrhythmias. It subsequently was found to be effective as a topical anesthetic and in the administration of regional and neuraxial anesthesia. Intravenous lidocaine has anti-inflammatory, analgesic, anti-hyperalgesic properties and is used for attenuating stress response to laryngoscopy and intubation.[10,12] Lidocaine (1.5mg/kg) blunts the sympathetic response during intubation, extubation and surgical stimulation.[12]

The purpose of our study is to see the effects of these three drugs in attenuation of the endotracheal intubation reflex. The result of the study is expected to help aneasthesia physicians to effectively manage hypertensive patients by reducing those cardiovascular complications due to endotracheal intubation reflex, and provide good anesthetic outcome, less hospital stays and reduced treatment cost by using those common drugs.

METHODS

This randomized controlled study was carried out in the Department of Anaesthesia, Analgesia and Intensive care Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between March and September of 2021. The patients included in the study were 18 between 70 years with previously diagnosed hypertension (became normotensive under antihypertensive drug while

participating in the study). However, patients receiving â-blockers or nitrates and had history of myocardial ischemia or infarction, cerebrovascular stroke, pulmonary, hepatic, and renal diseases were excluded. We used a convenient sampling technique. Finally, a total of 90 patients were included in the study based on our inclusion and exclusion criteria. The patients were randomly and equally allocated into three groups by computer generated random numbers, i.e., 30 in each group. Group A received inj. nitroglycerin 2 ìg/kg (diluted up to 5 ml in distilled water) 2 minutes before intubation, while group B received inj. labetalol 0.25 mg/kg (diluted up to 5 ml in distilled water) 5 minutes before intubation, and group C was the control group and received inj. 2% lidocaine 1.5 mg/kg (diluted up to 5 ml in distilled water) 2 minutes before intubation. Pre-anesthetic check-up was done in all the patients on the day before surgery. Patients on regular antihypertensive medication whose arterial blood pressure was d"140/90 during the preoperative anesthetic visit before surgery. On arrival of the patient in the operating room ASA standards monitoring system were attached with the patients and baseline parameters such as heart rate (HR), ECG, blood pressure (BP), respiratory rate, and oxygen saturation (SpO_2) were observed and recorded. Intravenous (IV) access was established with 18G cannula on non-dominant upper arm. All patients were pre-hydrated with 500 ml of Ringer's lactate solution. The Patients were pre-oxygenated with 100% oxygen for three minutes. Then the study drug was given as mentioned above. After that the patients were induced with Fentanyl 1.5 ìg/kg, 2.5% thiopental sodium 5mg/kg till the eyelash reflex was lost, followed by succinylcholine 1.5mg/kg IV to facilitate tracheal intubation. After the disappearance of fasciculation, laryngoscopy and intubation was done using standard Macintosh laryngoscope. The Patients were ventilated with 50% N_20 in 50% 02. Immediately after tracheal intubation, ECG, heart rate, systolic, diastolic, and mean arterial blood pressure (MAP), rate pressure product (RPP) was recorded as 0 minute. After 5 min, administration of volatile inhalational agent was started. The Patients were maintained on inhalational agent and a non-depolarizing muscle relaxant as per the need of the surgical procedure. At the end of surgery residual neuromuscular block was antagonized with intravenous inj. neostigmine 50ìg/kg and inj. atropine 20ìg/kg. Patients were observed for any side effects like hypotension, bradycardia, arrhythmias, and bronchospasm during the intraoperative period. If the patient developed hypotension, then treated with inj. Ephedrine and if the patient developed bradycardia, then he/she was treated with inj. atropine. Evaluation of the response to intervention: All haemodynamic parameters were recorded during the basal period, immediately after intubation (0 min), 1 minute, 2 minutes, and 5 minutes after intubation.

After multiple checks, data was recorded in a predesigned data collection sheet. Continuous variables were expressed as mean±SD and compared between groups by using unpaired student's t-test. Categorical variables were expressed as frequency and percentage and compared using the Chi-square test. The level of significance was at 95% confidence interval and a P-value <0.05 was considered as significant. Data were analyzed using SPSS (Statistical package for Social Sciences) version 22.0. The study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

RESULTS

Patients were randomly divided into three groups having 30 patients in each group. We observed the haemodynamic response before and after laryngoscopy and tracheal intubation after intravenous administration of nitroglycerin and labetalol. We considered group C as the control group who received standard lidocaine injection. The mean age of the patients was 44.4±10.9 years in group A, 47.6±9.4 years in group B and 46.4±10.6 years in group C. On consideration of weight, the patients had 61.2±7.3 kg, 62.5±6.7 kg and 63.6±5.4 kg respectively. No significant differences were observed in age, weight, sex and duration of laryngoscopy among those groups (P<0.05) (Table-I). There were no significant differences in heart rates (HR) among those groups before induction; however, in group B heart rate became lower than the other groups which was statistically significant at 0-minute, 1 minute, 2 minutes and 5 minutes (P<0.05). Heart rates were well maintained in all three groups; however, it was lowest in group B that received inj. labetalol (Table-II). Regarding the mean arterial pressure (MAP) between three groups which was significantly decreased in group A than group B and C at 0 minute (P<0.05). However, there was no significant difference (P>0.05) in case of MAP in other recordings at different time

intervals (Table-III). The rate pressure product (RPP) of the patients was significantly lower in group B at 1 minute, 2 minutes and 5 minutes except 0 minute than that of other two groups. RPP was also significantly lower in group A than that of group C at 0 minute (Table-IV). Regarding ECG changes at different times, sinus tachycardia was observed in 13.3%, 16.7% and 10% in group A, group B and group C respectively before induction. However, no other types of rhythm abnormalities were obserbved in any of the groups before induction. 26.7% of the patients in group A, 6.7% in group B and 20% in group C developed sinus tachycardia immediately after intubation; group B shows lower incidence of sinus tachycardia. In Group B, 10% after 1 minute, 13.3% patient after 2 minutes and 20% patient after 5 minutes developed sinus bradycardia, whereas it was 3.3%, 10% and 6.7% respectively in group C. No patient in group A had sinus bradycardia. 6.7% and 3.3% of the patients developed premature ventricular contractions after 1 minute of intubation in group A and group C respectively, while no patient in group B was found with premature ventricular contraction (Table-V).

Table-I: *Demographic characteristics of the patients and duration of laryngoscopy (n=90)*

Characteristics		Group A (n=30)	Group B (n=30)	Group C(n=30)	P value
Age (in years)		44.4±10.9	47.6±9.4	46.4±10.6	0.72
Weight (kg)		61.2±7.3	62.5±6.7	63.6±5.4	0.57
Gender	Male	18(60%)	16(53.4%)	20(66.67%)	0.69
	Female	12(40%)	14(47.6%)	10(33.33%)	0.65
Duration of Laryngoscopy (in seconds)		22.8±4.6	21.4±4.9	22.1±4.2	0.67

Table-II: *Comparison of heart rates of the patients (n=90)*

Heart rate (beat/min)	Group-A (n=30)	Group-B (n=30)	Group C (n=30)	P value A vs B	P value B vs C	P value C vs A
Before Induction	76.6±7.6	79.2±6.8	78.3±6.5	0.262	0.342	0.423
0 minute	79.7±7.3	69.3±5.5	80.8±6.7	0.005[s]	0.003[s]	0.321
1 minute	76.2±5.5	70.4±5.3	75.3±6.3	0.021[s]	0.028[s]	0.357
2 minutes	75.3±6.2	70.5±5.9	74.2±6.2	0.029[s]	0.029[s]	0.369
5 minutes	76.4±6.8	71.1±5.7	75.8±6.1	0.034[s]	0.037[s]	0.321

Table-III: *Comparison of mean arterial pressure (MAP) of the patients (n=90)*

Mean arterial pressure (mmHg)	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value A vs B	P value B vs C	P value C vs A
Before Induction	94.6±6.3	97.2±5.4	96.2±5.8	0.64	0.57	0.63
0 minute	86.3±7.1	92.6±5.5	90.8±4.8	0.014[s]	0.64	0.042[s]
1 minute	90.2±5.5	90.4±5.3	90.9±5.7	0.52	0.74	0.72
2 minutes	93.3±6.2	89.5±5.9	94.4±5.9	0.43	0.36	0.63
5 minutes	93.8±6.7	90.1±5.7	94.9±6.4	0.48	0.43	0.58

Table-IV: *Comparison of rate pressure product (RRP) of the patients (n=90)*

Rate pressure product	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value A vs B	P value B vs C	P value C vs A
Before Induction	11095.8±863	10970.2±880	11734.51±=882	0.43	0.53	0.61
0 minute	8889.6±931	8553.1±758	9934.6±834	0.36	0.023[s]	0.027[s]
1 minute	8983.7±859	7535.4±832	8625.6±925	0.018[s]	0.037[s]	0.34
2 minutes	9456.3±932	7342.5±892	8621.8±921	0.002[s]	0.019[s]	0.49
5 minutes	9763.5±976	7658.4±927	9261.3±989	0.004[s]	0.013[s]	0.53

S = statistically significant

Table- V: *ECG rhythm changes at various intervals (n=90)*

ECG Rhythm	Group A(n=30)			Group B(n=30)			Group C(n=30)			
	WNL	ST	PVC	WNL	ST	SB	WNL	ST	SB	PVC
Before induction	26(86.7%)	4(13.3%)	-	25(83.3%)	5(16.7%)	-	27(90%)	3(10%)		-
Just after ETI (0 minute)	20(66.6%)	8(26.7%)	2 (6.7%)	28(93.3%)	2(6.7%)	-	23(76.7%)	6(20%)		1(3.3%)
1 minute after ETI	22(73.3%)	8(26.7%)	-	26(86.7%)	1(3.3%)	3(10%)	26(86.7%)	3(10%)	1(3.3%)	-
2 minutes after ETI	24(80%)	6(20%)	-	25(83.3%)	1(3.3%)	4(13.3%)	24(80%)	3(10%)	3(10%)	-
5 minutes after ETI	29(96.7%)	1(3.3%)	-	24(80%)	-	6(20%)	25(83.3%)	3(10%)	2(6.7%)	-

Data was expressed as frequency and percentage. ETI: Endotracheal intubation; WNL: Within normal limit; ST: Sinus tachycardia; SB: Sinus bradycardia; PVC: Premature ventricular contraction

DISCUSSION

Endotracheal intubation reflex ensued by direct laryngoscopy technique results in transient changes mainly of cardiovascular, respiratory and central nervous physiology by reflex sympathetic stimulation and catecholamine discharge.[1,2] Hypertensive patients remain a concern for the anesthesia physician, as they are more prone to greater cardiovascular responses resulting more complications.[1,5] Hemodynamic response to laryngoscopy and intubation begins immediately after tracheal intubation and reaches maximum value within one minute. Therefore, timing of drug administration and their peak effect, used for attenuation of hemodynamic response, should correspond to those of hemodynamic response.[11]

The three groups of our study were comparable. The patients from labetalol group (group B) showed significantly lower heart rate in comparison to nitroglycerin and lidocaine at every interval after intubation. In the other two groups, there was no significant rise or fall of heart rate after intubation compared to baseline value. In our study, labetalol corroborates well with the findings of Kim et al. who reported that a single dose of labetalol of dosage 0.25 mg/kg given preoperatively 5 minutes before intubation decreases heart rate significantly after intubation up to 10 minutes.[13] Roelofse et al. found that labetalol of dosage 1 mg/kg given as i.v. bolus dose 1 min before laryngoscopy was not effective in the attenuation of heart rate.[14] This finding of that study can be explained by the different time of administration of the study drug because labetalol IV has onset of action at 2-3 min and has peak effect after 5 min.

However, the finding of heart rate in group B and group C of our study did not match with some previous studies as we observe no significant rise or fall of heart rate after intubation. They had documented that nitroglycerine does not attenuate the rise in heart rate after intubation which can be attributed to reflex tachycardia produced by vasodilation.[15,16] Regmi & Singh observed that nitroglycerine significantly decreases blood pressure, prevents rise in RPP but does not attenuate heart rate after endotracheal intubation.[17] These can be explained by difference in induction drugs, e.g., Mikawa et al. used IM atropine 0.01 mg/kg as premedication which could induce tachycardia,[15] while Grover et al. used glycopyrrolate 0.2 mg in all patient which could slightly rise the heart rate.[16] Both the studies used vecuronium to facilitate tracheal intubation, whereas in our study, we used succinylcholine 1.5 mg/kg which is a known drug that can cause bradycardia. The difference might be the cause of no significant rise in heart rate.

In our study, systolic blood pressure (SBP) was well controlled in all three groups; however, group B (labetalol) showed more sustained control than group C (lidocaine) and group A (nitroglycerin) group at all the time intervals after intubation. group B showed lower value of systolic blood pressure at 2 minutes and 5 minutes interval. The mean arterial pressure (MAP) was significantly decreased in group A at 0-minute but there was no significant difference in case of MAP at other time intervals. For systolic and mean arterial pressure the result of labetalol and lidocaine group corroborates with other recent studies. Jaiswal et al. showed that both lidocaine (1.5 mg/kg) and labetalol (0.25 mg/kg) effectively blunt the hemodynamic pressor response to endotracheal intubation and definitely have cardio protective action,[18] while Ratnani et al. reported that labetalol works better.[19] In our study systolic blood pressure was significantly lower in group A at 0 minute and 1

minute than two other group this can be explained by relative early onset of action and shorter duration of action of nitroglycerin. This finding is similar with the result of recent studies, Mikawa et al. reported single IV dose of nitroglycerin is a practical, effective, and safe method for attenuating the intubation induced hypertension.[15] Regmi & Singh showed nitroglycerin significantly decreases blood pressure, prevents rise of rate pressure product (RPP), but does not attenuate heart rate after endotracheal intubation.[17] Singh et al. reported that i.v. lidocaine 1.5 mg/kg is also an effective agent in suppressing hemodynamic response to laryngoscopy and intubation without any deleterious effect.[20]

In our study, RPP always remained below 12,000 in all three groups after intubation. In group B, RPP was the lowest throughout the post-intubation period. Nitroglycerin and lidocaine group also showed good control over rate pressure product throughout the study period. This finding confirms the cardio-protective effect of study drugs during laryngoscopy and intubation. It was showed that labetalol had more cardio-protective effect than nitroglycerin and lidocaine as the RPP was lower in labetalol group than two other groups. Swami et al. also found RPP in labetalol group was lower than that of other group at intubation, 1 min post intubation and onwards.[21] In another study done by Ratnani et al. showed mean RPP was most effectively attenuated by labetalol, whereas lignocaine showed least attenuation effect among their three study drugs.[19] It may be worth mentioning that nitroglycerine also showed similar response while used through sublingual route.[22]

In our study, among the three study drugs labetalol group showed better rhythm control in ECG as there was less incidence of tachycardia, rhythm abnormality like premature ventricular contraction was noted in group A (nitroglycerin) and group C (lidocaine). Incidence of tachycardia was highest in nitroglycerin group. Control of ECG rhythm in lidocaine group was better than nitroglycerin group as there was less incidence of tachycardia and premature ventricular contraction. This finding corroborates with other previous studies.[23,24] Besides, no cardiac dysrhythmias were noted in the study with labetalol.

In this study, we observed some of the haemodynamic variables (heart rate, blood pressure and rate pressure product) and electrocardiographic rhythm changes in hypertensive patients treated with study drugs. However, respiratory, hormonal, and central nervous system changes were not measured. With both intra and inter-group comparison all three drugs were effective for the attenuation of heart rate, systolic blood pressure, mean arterial pressure and rate pressure product after endotracheal intubation through direct laryngoscopy.

CONCLUSION

All three medications were effective in attenuation of direct laryngoscopic intubation reflex. The hemodynamic parameters such as heart rate, blood pressure, rate pressure product and elertrocardiographic rhythm changes were relatively more stable in labetolol group as compared to nitroglycerin and lidocaine. To summarize, labetalol is safer and more effective than nitroglycerin and lidocaine to attenuate the endotracheal intubation reflex in hypertensive patients.

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