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Research Article

Attenuation of hemodynamic response to laryngoscopy and endotracheal intubation with two different doses of labetalol in hypertensive patients

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KEYWORDS

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Abstract *Purpose:* The present study compared the efficacy of two different doses of labetalol, for attenuation of hemodynamic response to laryngoscopy and intubation in hypertensive patients.
Patients and methods: 75 hypertensive patients, aged 18–60 years undergoing elective surgical procedures, require general anesthesia and orotracheal intubation. Patients were allocated to any of the three groups (25 each), Group C (control) 5 ml 0.9% saline. Group L1 (labetalol) 0.15 mg/kg diluted with 0.9% saline to 5 ml. Group L2 (labetalol) 0.3 mg/kg diluted with 0.9% saline to 5 ml. In the control group 5 ml of 0.9% saline was given i.v. 5 min prior to intubation. In the L1 group 0.15 mg/kg of labetalol was given i.v. 5 min prior to intubation. In the L2 group 0.3 mg/kg of labetalol was given i.v. 5 min prior to intubation. All the patients were subjected to the same standard anesthetic technique. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded prior to induction, at time of intubation and 1, 3, 5, and 10 min after intubation. Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated.
Results: Compared to placebo both the doses of labetalol (0.15 mg/kg) and (0.3 mg/kg) significantly attenuated the rise in heart rate, systolic blood pressure, and RPP during laryngoscopy and intubation. However, the difference was not statistically significant between both doses of labetalol at intubation, 1 min, 3 min and 10 min post-intubation.
Conclusion: Both doses of labetalol (0.15 mg/kg and 0.3 mg/kg) attenuate hemodynamic response to laryngoscopy and intubation in dose dependent manner.

1. Introduction

Increases in heart rate and blood pressure are the principal changes in the cardiovascular system during laryngoscopy and tracheal intubation. Stimulus of the laryngeal and tracheal

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tissues may also cause increases in both sympathetic and sympatho-adrenal reflex activities [1,2]. Hemodynamic changes are generally temporary without any sequelae. However, these changes can facilitate and accelerate the development of myocardial ischemia, arrhythmia, infarction and cerebral hemorrhage in patients with coronary artery disease, hypertension or cerebrovascular disease [3,4]. Different pharmacologic agents such as lidocaine, vasodilator agents inhibiting sympatho-adrenal response, α- and ß-adrenergic blockers, opioids and calcium channel blockers can be administered prior to tracheal intubation in order to prevent hemodynamic responses [5–10].

Labetalol is an unique oral and parenteral antihypertensive drug that is α1- and nonselective β1- and β2-adrenergic antagonist. It reaches its peak effect at 5–15 min after intravenous (IV) injection and rapidly redistributes (5.9 min redistribution half-life). It lowers BP by decreasing systemic vascular resistance (α1-blockade), whereas reflex tachycardia triggered by vasodilatation is attenuated by simultaneous β-blockade. Cardiac output remains unchanged [11–19]. The aim of the present study was to compare the efficacy of two different doses of labetalol for controlling these hemodynamic responses to laryngoscopy and tracheal intubation under the same anesthetic techniques in hypertensive patients.

2. Patients and methods

This study was a prospective, randomized, placebo controlled, double-blinded trial comparing two different doses of labetalol in decreasing the hemodynamic response during rigid laryngoscopy and intubation. The protocol was approved by the Institutional Review Board and was in accordance with International Conference on Harmonization; Good Clinical Practice (ICH-GCP) standards.

Sample size was calculated by power analysis, using a two-sample *t* test, with a two-sided type I error of 5% ($\alpha = 0.05$) and power at 80.37 ($\alpha = 0.19$). Therefore, 75 patients, ASA physical status I and II, aged 18–60 years, undergoing elective surgical procedures, requiring general anesthesia and orotracheal intubation were included in the study. Informed consent was obtained from all the patients. According to the diagnostic criteria of the Joint National Committee on Hypertension (JNC-8), hypertension was defined if systolic blood pressure was >140 mmHg and/or diastolic blood pressures were >90 mmHg. During pre-anesthetic evaluation patients were identified who are hypertensive but their hypertension was controlled by antihypertensive drugs such as calcium channel antagonists (e.g., nifedipine, nicardipine, diltiazem) and renin-angiotensin inhibitors (e.g., captopril) for varying periods of time. None had a history of myocardial ischemia or infarction, nor had an abnormal ECG on admission to the hospital. Patients with cardiovascular, pulmonary, hepatic, and renal disease; those on B blockers; patients with difficult airway; laryngoscopy and intubation time more than 20 s, or requiring more than two attempts were excluded from the study.

The patients were randomly (computer generated randomization schedule) allocated into one of the three groups, of 25 each. Blinding was done using the sequentially numbered opaque sealed envelope (SNOSE) technique. Patients were kept nil orally for 8 h prior to surgery and morning dose of antihypertensive drugs was given at 6 am with sips of water on the day of the surgery. All patients were premedicated intravenously 10 min prior to induction with inj. ondansetron 0.1 mg/kg, and inj. midazolam 0.05 mg/kg. In a double blind manner, one 5 ml syringe was prepared for each patient.

Group L1 – Syringe contained Labetalol (0.15 mg/kg diluted with 0.9% saline to 5 ml).
Group L2 – Syringe contained Labetalol (0.3 mg/kg diluted with 0.9% saline to 5 ml).
Group C – Syringe contained 5 ml of 0.9% saline.

After recording the baseline parameters, patients were pre-oxygenated with 100% O_2 by a face mask for 3 min and then study drug was administered *iv* five minutes before intubation. Anesthesia was induced with 5 mg kg^{-1} thiopentone *iv*, and loss of the eyelash reflex was confirmed followed by 0.1 mg kg^{-1} vecuronium *iv*. Direct laryngoscopy with a standard Macintosh laryngoscope blade for tracheal intubation was initiated five minute after administration of study drug. None received topical lidocaine and opioids before laryngoscopy for tracheal intubation. All intubations were performed by the first author, and were accomplished within 20 s. Tracheal tubes of ID 7.0 mm and 8.0 mm were used for female and male patients, respectively. After tracheal intubation, anesthesia was maintained with 4 L min^{-1} nitrous oxide, 2 L min^{-1} oxygen and isoflurane 1.0% and intermittent boluses of I mg vecuronium bromide. Manual ventilation of the lungs was adjusted to maintain an end-tidal CO_2 tensions between 35 mmHg and 40 mmHg as measured by an anesthetic/respiratory gas analyzer (AS/3™, Datex, Helsinki, Finland). At the end of surgery, neuromuscular blockade was reversed with inj. neostigmine (40 μg/kg) and inj. glycopyrrolate (10 μg/kg). Heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded prior to induction, at time of intubation and 1, 3, 5, and 10 min after intubation. Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated for the same time stations. Abnormal ECG changes were also recorded.

2.1. Statistical analysis

Statistical analysis was performed using the SPSS software version 20 (Chicago, IL, USA). Patient demographics were compared with analysis of variance (ANOVA). The study data were analyzed using statistical methods of mean, standard deviation, paired students "*t*" test (for values within the group at different time stations) and independent samples "*t*" test (for comparison of intergroup values). All values were expressed as mean ± SD. $P < 0.05$ was considered as significant (*S*) and $P > 0.05$ as statistically non-significant (NS).

3. Results

The patients in the three groups were comparable with respect to age, weight, sex, and duration of surgery or anesthesia (Table 1).

The pre-induction values of heart rate (HR) were comparable between groups with no significant difference (Table 2). There was statistically significant difference in HR throughout study time between the L1 and control group ($P < 0.001$), and L2 and control group ($P < 0.001$). At intubation, 1 min, 3 min

Table 1 Demographic data.

	Group L1 (n = 25)	Group L2 (n = 25)	Group C (n = 25)
Age (yr)	42 ± 10	41 ± 12	42 ± 12
Sex (female/male)	18/7	19/6	19/6
Height (cm)	155 ± 10	156 ± 12	154 ± 11
Weight (kg)	52 ± 10	51 ± 11	50 ± 11
Antihypertensive medication			
– Calcium channel blocker	13	10	11
– Renin-angiotensin inhibitor	12	15	14

Mean values ± SD or number. L1 = labetalol (0.15 mg/kg), L2 = labetalol (0.3 mg/kg) C = control.

and 10th minute post intubation HR was not statistically significantly different in the L1 and L2 group ($P > 0.05$). At 5 min post intubation, there was significant difference in HR between L1 and L2 groups ($P < 0.001$).

The pre-induction values of SBP were comparable between groups with no significant difference (Table 3). Compared with the control group values SBP was significantly lower at all time stations in the L1 ($P < 0.001$) and L2 group ($P < 0.001$). There were no significant difference in SBP between L1 and L2 at intubation and 1 min post-intubation ($P > 0.05$). However, there was statistically significant difference in SBP between L1 and L2 group at 3 min, 5 min and 10 min post intubation ($P < 0.001$).

The pre-induction values of DBP were comparable between groups with no significant difference (Table 3). Compared with the control group values DBP was significantly lower at all time stations in the L1 ($P < 0.001$) and L2 group ($P < 0.001$). There was no significant difference in DBP between L1 and L2 at intubation and 1 min post-intubation. However, there was statistically significant difference in DBP between L1 and L2 group at 3 min, 5 min and 10 min post intubation ($P < 0.001$) (see Table 4).

The pre-induction values of MAP were comparable between groups with no significant difference (Table 5). MAP was significantly high at the time of intubation in the control group compared with L1 ($P < 0.001$) and L2 group ($P < 0.001$). Intubation and 1 min post intubation values were comparable between the L1 and L2 group and not statistically significant ($P > 0.05$). However, there were statistically significant difference in MAP values between L1 and L2 group at 3 min, 5 min and 10 min post intubation ($P < 0.001$).

The pre-induction values of RPP were comparable between groups with no significant difference (Table 6). RPP was significantly less at the time of intubation in the L1 and L2 group ($P < 0.001$) as compared to the control group. Intubation and 1 min post intubation values were comparable between the L1 and L2 group and not statistically significant ($P > 0.05$). However, there was statistically significant difference in RPP values between L1 and L2 group at 3 min, 5 min and 10 min post intubation ($P < 0.00$).

4. Discussion

Hypertensive patients are more prone to greater cardiovascular responses to laryngoscopy and tracheal intubation than are normotensive patients. Fox et al. reported two hypertensive patients in whom complications, including pulmonary edema, cardiac failure and cerebrovascular hemorrhage, followed hypertensive episodes directly related to tracheal intubation. Thus, transitory increases in AP and HR are probably of no consequence in healthy individuals, but either or both may be dangerous to those with hypertension, myocardial insufficiency, or cerebrovascular disease. Therefore, the prevention of these hemodynamic changes following tracheal intubation is of particular importance in hypertensive patients [3,9–11].

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. The onset of action of labetalol 2–3 min and peak effect reaches at 5–15 min [14]. We studied the hemodynamic response to laryngoscopy and intubation for a period of 10 min as this is the average period for which hemodynamic response to laryngoscopy and intubation are believed to last [14,16].

The adverse cardiovascular changes and catecholamine discharge seen during laryngoscopy and tracheal intubation appear in two phases. The effects of laryngoscopy should be distinguished from effects seen while the endotracheal tube is placed through the trachea. Shribman et al. showed the differences between these two events. Even with stable anesthesia, laryngoscopy alone without intubation can cause a supraglottic stimulus. As a result, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase in contrast to the measurements before induction. However, no significant increase in HR occurs during laryngoscopy. Increase in BP is due to norepinephrine, while increase in HR is due to epinephrine discharge. Infraglottic stimulus caused by placing

Table 2 Heart rate.

HR	Group C	Group L1	Group L2	P value C & L1	P value C & L2	P value L2 & L1
Pre-induction	83.64 ± 6.0	82.44 ± 6.3	84.24 ± 6.4	($P > 0.05$)	($P > 0.05$)	($P > 0.05$)
At intubation	109.40 ± 6.3	96.20 ± 7.0	93.72 ± 5.6	$P < 0.001$	$P < 0.001$	($P > 0.05$)
I min post-intubation	104.20 ± 6.1	96.24 ± 6.5	94.40 ± 5.2	$P < 0.001$	$P < 0.001$	($P > 0.05$)
3 min post-intubation	93.64 ± 4.4	88.08 ± 6.2	86.68 ± 5.3	$P < 0.001$	$P < 0.001$	($P > 0.05$)
5 min post-intubation	86.36 ± 3.4	81.60 ± 6.3	75.04 ± 10.9	$P < 0.001$	$P < 0.001$	$P < 0.001$
10 min post-intubation	78.60 ± 4.5	72.16 ± 6.8	69.04 ± 9.9	$P < 0.001$	$P < 0.001$	($P > 0.05$)

Mean value ± SD.

Table 3 Systolic blood pressure.

SBP	Group C	Group L1	Group L2	*P* value C & L1	*P* value C & L2	*P* value L2 & L1
Pre-induction	132 ± 5.5	131.44 ± 1.5	133.04 ± 5.0	($P > 0.05$)	($P > 0.05$)	($P > 0.05$)
At intubation	162.16 ± 13.0	145.88 ± 6.7	144.88 ± 6.0	$P < 0.001$	$P < 0.001$	($P > 0.05$)
I min post intubation	152.72 ± 12.0	139.96 ± 5.4	136.80 ± 5.8	$P < 0.001$	$P < 0.001$	($P > 0.05$)
3 min post-intubation	140.92 ± 8.3	131.68 ± 5.2	121.80 ± 9.4	$P < 0.001$	$P < 0.001$	$P < 0.001$
5 min post-intubation	136.28 ± 5.6	123.24 ± 8.6	111.92 ± 11.6	$P < 0.001$	$P < 0.001$	$P < 0.001$
10 min post-intubation	129.64 ± 6.6	111.60 ± 8.2	104.20 ± 7.0	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean value ± SD.

Table 4 Diastolic blood pressure.

DBP	Group C	Group L1	Group L2	*P* value C & L1	*P* value C & L2	*P* value L2 & L1
Pre-induction	82.60 ± 5.2	82.40 ± 5.0	81.72 ± 4.9	($P > 0.05$)	($P > 0.05$)	($P > 0.05$)
At intubation	102.56 ± 3.8	93.0 ± 5.1	91.0 ± 5.2	$P < 0.001$	$P < 0.001$	($P > 0.05$)
I min post-intubation	104.40 ± 7.9	89.48 ± 8.4	86.40 ± 11.4	$P < 0.001$	$P < 0.001$	($P > 0.05$)
3 min post-intubation	114.01 ± 4.1	100.56 ± 86.8	93.21 ± 7.0	$P < 0.001$	$P < 0.001$	$P < 0.001$
5 min post-intubation	94.28 ± 5.6	81.88 ± 4.4	71.36 ± 9.3	$P < 0.001$	$P < 0.001$	$P < 0.001$
10 min post-intubation	82.20 ± 7.5	72.84 ± 5.2	67.88 ± 7.5	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean value ± SD.

Table 5 Mean arterial pressure.

MAP	Group C	Group L1	Group L2	*P* value C & L1	*P* value C & L2	*P* value L2 & L1
Pre-induction	99.25 ± 4.6	98.75 ± 4.5	98.83 ± 4.4	($P > 0.05$)	($P > 0.05$)	($P > 0.05$)
At intubation	122.43 ± 6.0	110.63 ± 4.9	108.96 ± 4.4	$P < 0.001$	$P < 0.001$	($P > 0.05$)
I min post-intubation	120.51 ± 7.6	106.31 ± 5.4	103.20 ± 8.4	$P < 0.001$	$P < 0.001$	($P > 0.05$)
3 min post-intubation	114.01 ± 4.1	100.19 ± 8.6	93.21 ± 7.0	$P < 0.001$	$P < 0.001$	$P < 0.001$
5 min post-intubation	108.28 ± 4.7	95.67 ± 4.0	84.88 ± 8.8	$P < 0.001$	$P < 0.001$	$P < 0.001$
10 min post-intubation	98.00 ± 6.0	85.64 ± 4.4	80.00 ± 6.3	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean value ± SD.

Table 6 Rate pressure product (RPP).

RPP	Group C	Group L1	Group L2	*P* value C & L1	*P* value C & L2	*P* value L2 & L1
Pre-induction	11097.12 ± 993.9	10835.12 ± 921.5	11200.88 ± 878.0	($P > 0.05$)	($P > 0.05$)	($P > 0.05$)
At intubation	17756.48 ± 1948.2	14037.28 ± 1279.0	13571.20 ± 895.4	$P < 0.001$	$P < 0.001$	($P > 0.05$)
I min post-intubation	15936.16 ± 1766.5	3455.92 ± 861.94	12911.20 ± 875.3	$P < 0.001$	$P < 0.001$	($P > 0.05$)
3 min post-intubation	13210.44 ± 1179.0	11596.32 ± 927.3	10565.44 ± 1116.9	$P < 0.001$	$P < 0.001$	$P < 0.001$
5 min post-intubation	11771.36 ± 717.7	10062.40 ± 1125.8	8481.20 ± 1787.5	$P < 0.001$	$P < 0.001$	$P < 0.001$
10 min post-intubation	10185.04 ± 741.1	8054.24 ± 974.4	7219.68 ± 1290.5	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean value ± SD.

the endotracheal tube occurs in phase two. In this situation, an extra cardiovascular response and catecholamine discharge occur. Stress response increases at this stage and both SBP and DBP measurements increase by 36–40% in contrast to control levels. HR levels increase more than 20% with tracheal intubation in contrast to laryngoscopy [20–21].

The present study has demonstrated that *iv* administration of labetalol in two different doses attenuates the increases in MAP and RPP after laryngoscopy and tracheal intubation. Levels of RPP > 20,000 are more commonly associated with angina and myocardial ischemia [9]. In the present study, the RPP after tracheal intubation was 17756.48 in Group C (Table 6), but these critical increases in RPP were avoided in Groups L1 and L2. Furthermore, the changes from baseline values in RPP immediately after tracheal intubation in Group L1 and L2 were significantly less than those in Group C. The

differences in these changes of RPP following tracheal intubation may be attributed to the differences in those of HR. Tachycardia causes more stress effect on the heart than increases in BP. This effect can be due to the increase in myocardial oxygen requirement, decreased diastolic filling, and reduction in the time needed for effective coronary circulation. Tachycardia accompanied with hypertension increases the existing ischemia risk in patients with coronary artery disease [9].

Values of group L1 and L2 when compared with their preoperative values (Tables 2 and 5) show insignificant rise ($P > 0.05$) in heart rate and MAP at the time of intubation as compared to placebo group. Increases in HR and MAP at intubation in the placebo group were 30% and 23%, respectively, in the L1 group, 16% and 12% and L2 group 11% and 11% respectively. Our results corroborate well with the finding of Amar et al. who administered 0.15 mg/kg of labetalol for induction and 0.25–0.3 mg/kg for maintenance of anesthesia in a study investigating its effects on perioperative stress. Increases in HR and MAP at intubation in the placebo group were 33% and 52%, respectively, and in the labetalol group, 7.3% and 21.3%, respectively [22]. Kim et al. reported that a single dose of labetalol of dosage 0.25 mg/kg given preoperatively 5 min before intubation decreases HR significantly after intubation up to 10 min [17]. Roelofse et al. found that labetalol of dosage 1 mg/kg given as an IV bolus 1 min before laryngoscopy was not effective in the attenuation of HR. This failure of the study can be explained by the different time of administration of the study drug because labetalol has peak effect after 5–10 min [23].

There was statistically significant difference in HR between L1 and L2 group at 5 min post intubation ($P < 0.00$). Similarly, there was statistically significant difference in SBP, DBP, MAP and RPP between L1 and L2 group at 3 min, 5 min and 10 min post intubation ($P < 0.00$). These may because of higher dose of labetalol used in L2 (0.3 mg/kg) group as compared to L1 (0.15 mg/kg) group.

The only side effect observed was that of group L2 (0.3 mg/kg) in form of bradycardia, intraoperatively. Seven patients (28%) developed bradycardia (pulse rate < 50 beats per minute) after the study period of 10 min and atropine in 0.2 mg increments (max. 0.01 mg/kg) was given. All the patients responded to atropine treatment. There were no recurrent episodes of bradycardia. Transient premature ventricular contractions appeared immediately after tracheal intubation in two patients who received placebo saline. These arrhythmias did not need any treatment. Thus, there were no serious complications after laryngoscopy and tracheal intubation in patients who had received labetalol at both the doses. To conclude, Labetalol in both the doses 0.15 mg/kg *and* 0.3 mg/kg *iv* is effective in reducing the hemodynamic responses to direct laryngoscopy and tracheal intubation in dose dependent manner in hypertensive patients. However bradycardia is more common in patients who are receiving labetalol in dose of 0.3 mg/kg. Further studies are needed to elucidate the comparative effects of both doses of labetalol in large number of patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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