EFFECTIVENESS OF INJECTION LABETALOL IN TWO DIFFERENT DOSAGES FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO DIRECT LARYNGOSCOPY AND ORAL ENDOTRACHEAL INTUBATION: A RANDOMISED DOUBLE BLIND TRIAL

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ABSTRACT

PURPOSE

To compare the efficacy of two different doses of labetalol for attenuation of haemodynamic response during laryngoscopy and endotracheal intubation - A randomised control trail.

MATERIALS AND METHODS

90 patients of either sex, aged 18–60 years, of ASA (American Society of Anaesthesiologist) class I or II, posted for elective surgical procedures requiring general anaesthesia with intubation were selected. Patients were randomly allocated to any of the three groups (30 each). In Group C, i.e. control group, 5 mL 0.9% saline; in Group L1, Inj. Labetalol 0.1 mg/kg diluted with 0.9% saline with total volume of 5 mL; and in Group L2, Inj. Labetalol 0.2 mg/kg was diluted with 0.9% saline with total volume of 5 mL. The study drug was administered to subjects intravenously 5 min. prior to intubation. All the patients were subjected to the same standard anaesthetic technique. The vital parameters i.e. heart rate, systolic blood pressure and diastolic blood pressure were recorded, mean arterial pressure was calculated prior to induction at time of intubation and 1 min., 3 min., 5 min., and 10 min. after intubation.

RESULTS

A significant attenuation response of haemodynamics was seen in group L1 and L2 when compared to control group C. No significant difference was observed between the group L1 and L2 at intubation, 1 min., 3 min., 5 min. and 10 min. post-intubation.

CONCLUSION

Both doses of Inj. Labetalol (0.1 mg/kg and 0.2 mg/kg) attenuate haemodynamic response to laryngoscopy and intubation in dose dependent manner.

KEYWORDS

Labetalol, HR, MAP, Laryngoscopy and Tracheal Intubation.

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INTRODUCTION: One of the challenges to anaesthesiologist is to prevent stress response during laryngoscopy and endotracheal intubation. The sympathetic system outflow increases once laryngeal and tracheal tissues are stimulated.[1,2] Usually haemodynamic changes are generally temporary without any sequelae in healthy adults. Because of these haemodynamic changes patients who are at risk may develop myocardial ischaemia, arrhythmia, infarction and cerebral haemorrhage.[3,4] Various intravenous pharmacologic drugs i.e. lidocaine, vasodilators, ß-adrenergic blockers, opioids and calcium channel blockers are successfully tried and proved to be effective if administered prior to laryngoscopy and tracheal intubation.[5–10]

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Inj. Labetalol is a α1 and nonselective β adrenergic receptor, which is available in both oral and parenteral formulation. This is the drug used as an antihypertensive during accelerated hypertension treatment. After intravenous (IV) injection, the peak effect of the drug is observed at 5–15 min. It has rapid redistribution half-life time of 5.9 min. The blood pressure lowering effect is seen mainly due to its a1 adrenergic receptor blockade, hence reducing peripheral vascular resistance. Due to vasodilatation the reflex tachycardia is observed and is attenuated by simultaneous β adrenergic receptor blockade. Overall effect on cardiac output remains unchanged.[11–19] The aim of the present study was to study and compare the efficacy of intravenous Inj. labetalol in two different doses on haemodynamic responses to laryngoscopy and tracheal intubation in normotensive adult patients.

MATERIALS AND METHODS: Before conducting the research, an institutional ethical committee approval was obtained. After getting informed consent, study was

conducted on 90 adult patients satisfying inclusion criteria. Inclusion criteria include patients aged between 18 years to 60 years, of either sex with ASA class I and II posted for elective general surgery requiring general anaesthesia with tracheal intubation. The exclusion criteria was any patients who are not willing to participate in the study, patients with difficult airway, known hypertensive and/or autonomic dysfunction or any other cardiovascular comorbid illness.

Sample size of 90 was obtained using a two sample t test, a two-sided type I error of 5% (a =0.05) and power at 80.37 (a= 0.19). A computer generated randomisation was done for allotment of patient in any of the three groups.

All 90 patients were grouped into 3 groups i.e. in group C, syringe was loaded with 5 mL of 0.9% saline; in group L1, syringe was loaded with Inj. Labetalol (0.1 mg/kg diluted with 0.9% saline to make a total volume of 5 mL); in group L2, syringe was loaded with Inj. Labetalol (0.2 mg/kg diluted with 0.9% saline to make a total volume of 5 mL).

The drug was prepared by the person who is not involved in the study. The patient and the person recording the parameters are blinded from the study drug. Patients were kept nil orally for 6 hrs. prior to surgery. All patients received intravenous Inj. Ondansetron 0.1 mg/kg as antiemetic, and Inj. midazolam 0.05 mg/kg as sedation 10 min. prior to induction as premedication as per our institutional protocol.

Baseline parameters, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and calculated mean arterial blood pressure (MAP) are recorded before inducing the patient with general anaesthesia. After premedication, patients were pre-oxygenated with 100% oxygen for 5 minutes. The study drug was administered IV depending upon group allotment just five minutes before intubation. Anaesthesia was induced with IV Inj. Thiopentone (5 mg/kg) and intubation was facilitated with Inj. Vecuronium 0.1 mg/kg. After direct laryngoscopy, orotracheal intubation with appropriate size cuffed endotracheal tube insertion was done. All intubations were performed by the first author, and were performed within 20 sec. After confirmation of the endotracheal insertion, the anaesthesia was maintained with nitrous oxide (4L/min.) and oxygen (2L/min.) and Halothane 1.0% as inhalational agent with intermittent boluses of Inj. vecuronium. Manual ventilation of the lungs was done keeping end-tidal concentration of carbon dioxide at 35- 45 mmHg. At the end of surgery, neuromuscular blockade was reversed with Inj. Neostigmine (0.5 mg/kg) and Inj. Glycopyrrolate (0.008 mg/kg). HR, SBP and DBP were recorded prior to induction, at time of intubation and 1 min., 3 min., 5 min., and 10 min. after intubation. Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated accordingly for all the time intervals mentioned above. Abnormal ECG changes if any observed during the study were also noted.

STATISTICAL ANALYSIS: Patient demographic parameters were compared using analysis of variance (ANOVA) test. For values within the group at different time stations, mean, standard deviation, paired students "t" test and for independent samples "t" test to compare intergroup values was done. The values were expressed as mean ± SD and P value < 0.05 was considered as significant (S) and > 0.05 considered as statistically non-significant (NS).

RESULTS: All patients in three groups were comparable with respect to age, sex, weight, and total duration of surgery and anaesthesia (Table 1).

	Group L1	**Group L2**	**Group C**
Age	38±10	37±10	38±10
Sex	15/15	15/15	15/15
Height	150±10	149±10	149±10
Weight	50±10	50±10	50±10

Table 1

The pre-induction values of HR were comparable between all three groups with no statistically significant difference (Table 2).

A statistically significant difference in HR observed throughout the study time between group L1 and control group (P< 0.001), also between group L2 and control group (P <0.001). At intubation, 1 min., 3 min. and 10 minutes post-intubation HR was not statistically significantly different in group L1 and group L2 (P > 0.05). At 5 min. post-intubation, there was significant difference in HR between group L1 and group L2 (P < 0.001). The pre-induction values of SBP were comparable between groups with no significant difference (Table 3). The SBP values were significantly lower in group L1 (P <0.001) and L2 (P <0.001) when compared to control group C in all the time intervals. When SBP is compared between the group L1 and L2 at intubation and 1 min. post-intubation period the values are not statistically significant (P > 0.05). There was a statistically significant difference in SBP between group L1 and group L2 group at 3 min., 5 min. and 10 min. post-intubation (P < 0.001) period. The pre-induction values of DBP were comparable between all three groups with no statistical significant difference (Table 3). When compared with the control group, DBP values are significantly lower at all times in group L1 (P< 0.001) and L2 group (P <0.001). At intubation and 1 min. post-intubation, no statistical significant difference was observed in DBP between groups L1 and L2. As shown in table 4, at 3 min., 5 min. and 10 min. post-intubation, there was a significant DBP value difference observed between group L1 and L2. (P < 0.001). The table 5 shows pre-induction MAP values wherein the values are comparable between groups. The MAP values are significantly high at the time of intubation in control group i.e. in group C when compared with group L1 (P < 0.001) and group L2 (P <0.001). There were no statistically significant (P > 0.05) MAP values noted at intubation and 1 min. post-intubation but were comparable between the group L1 and group L2. There is a statistically significant difference in MAP values between L1 and L2 group at 3 min., 5 min. and 10 min. post-intubation (P < 0.001). Intubation and 1 min. post-intubation values were comparable between group L1 and group L2 but are not statistically significant (P> 0.05).

DISCUSSION: In general anaesthesia with endotracheal intubation, a stress response due to sympathoadrenal outflow is commonly observed. This response is seen during laryngoscopy and intubation due to stimulation of laryngeal and tracheal tissues. Such response is usually well tolerated by normotensive patients. Hypertensive patients are more prone to complications due to such response. In a report, Fox et al. noticed two hypertensive patients faced the complications including pulmonary oedema, cardiac failure and intracranial haemorrhage following hypertensive episodes which were actually related to tracheal intubation. In case of healthy normal individuals, this transient rise in HR and MAP probably does not face such risks. The prevention of such stress response following tracheal intubation is paramount important in hypertensive patients [3,9–11]. The change in haemodynamic response initiated immediately after tracheal intubation and reaches to maximum level within one minute. Hence, the timing of drug selected to attenuate stress response should correspond to peak effects of the drug. The onset of action of labetalol is usually 2 min. and its peak effect reaches at 5 min. to 15 min. [14]. In this study, the haemodynamic response to laryngoscopy and intubation for a period of 10 min. was studied. This is mainly due to the average period for stress induced during laryngoscopy and intubation are believed to last for 10 min.[14,16] There are two phases of release of catecholamines by sympathoadrenal stimulation which occurs during laryngoscopy and intubation. These two phases are during laryngoscopy and during the endotracheal tube placement. The author Shribman et al. in his study showed the differences between these two events. Supraglottic stimulation was observed even during stable anaesthesia where in laryngoscopy was performed. The rise in both SBP and DBP observed in contrast to the measurements before induction. There is no significant HR noted during laryngoscopy. The increase in BP and HR are mainly due to norepinephrine and epinephrine discharge respectively.

Mean values± SD or number. L1= labetalol (0.1 mg/kg), L2=labetalol (0.2 mg/kg), C=control.

HR	Group C	Group L1	Group L2	P value C & L1	P value C & L2	P value L2 & L1
Pre-induction	83.64±6	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)

Table 2: Heart Rate

Mean value± SD.

SBP Group C	Group L1	Group L2	P value C & L1	P value C & L2	P value L2 & L1	
Pre-induction	112±5.5	111.44± 1.5	113.04±5.0	(P >0.05)	(P> 0.05)	(P >0.05)
At intubation	132.16±13.0	125.88± 6.7	124.88±6.0	P<0.001	P <0.001	(P >0.05)
1 min. post intubation	132.72±12.0	119.96± 5.4	116.80±5.8	P<0.001	P <0.001	(P >0.05)
3 min. post-intubation	120.92±8.3	111.68± 5.2	101.80±9.4	P<0.001	P <0.001	P <0.001
5 min. post-intubation	116.28±5.6	103.24± 8.6	91.92±11.6	P<0.001	P <0.001	P <0.001
10 min. post-intubation	109.64±6.6	91.60± 8.2	84.20±7.0	P<0.001	P <0.001	P <0.001

Table 3: Systolic Blood Pressure

Mean value±SD.

DBP	Group C	Group L1	Group L2	P value C & L1	P value C & L2	P value L2 & L1
Pre-induction	67±5.2	67.40±5.0	66.72±4.9	(P >0.05)	(P >0.05)	(P >0.05)
At intubation	87.56±3.8	78.0 ±5.1	76.0 ±5.2	P <0.001	P <0.001	(P >0.05)
1 min. post-intubation	88.40±7.9	74.48±8.4	71.40±11.4	P <0.001	P <0.001	(P >0.05)
3 min. post-intubation	99.01±4.1	85.56±86.8	78.21±7.0	P <0.001	P <0.001	P <0.001
5 min. post-intubation	79±5.6	68.88±4.4	58.36±9.3	P <0.001	P <0.001	P <0.001
10 min. post-intubation	67.20±7.5	60.84±5.2	55.88±7.5	P <0.001	P <0.001	P <0.001

Table 4: Diastolic Blood Pressure

Mean value±SD.

MAP	Group C	Group L1	Group L2	P value C & L1	P value C & L2	P value L2 & L1
Pre-induction	82.25± 4.6	81.75±4.5	81.83±4.4	(P>0.05)	(P >0.05)	(P >0.05)
At intubation	105.43± 6.0	93.63±4.9	91.96±4.4	P< 0.001	P< 0.001	(P >0.05)
1 min. post-intubation	103.51± 7.6	89.31±5.4	86.20±8.4	P< 0.001	P< 0.001	(P >0.05)
3 min. post-intubation	97.01± 4.1	83.19±8.6	76.21±7.0	P< 0.001	P< 0.001	P <0.001
5 min. post-intubation	91.28± 4.7	78.67±4.0	67.88±8.8	P< 0.001	P< 0.001	P <0.001
10 min. post-intubation	81.00± 6.0	68.64±4.4	63.00±6.3	P< 0.001	P< 0.001	P <0.001

Table 5: Mean Arterial Pressure

Mean value±SD.

The phase two is observed during infraglottic stimulus which occurs due to the placement of endotracheal tube in phase two. An additional cardiovascular response and catecholamine discharge occurs during this phase. During this stage, stress response increases SBP and DBP by 36–40% in comparison with control group readings. The rise in HR levels is more than 20% with tracheal intubation in contrast to laryngoscopy.[20–21] The result of the present study has demonstrated IV administration of Inj. Labetalol in either dose i.e. 0.1 mg/kg or 0.2 mg/kg in pre-induction time attenuates the stress response which is caused due to direct laryngoscopy and orotracheal intubation. Always the tachycardia causes more stressful effect on the heart when compared to rise in BP as tachycardia increases myocardial oxygen demand, also decreases diastolic filling period, and may lead to myocardial infarction as there will be reduction in the time needed for coronary circulation. Tachycardia when seen in pre-existing hypertensive patients increases the risk of myocardial infarction and or ischaemia.[9] The rise in heart rate from the preoperative values are insignificant (P >0.05) in group L1 and L2 when compared to control group (Tables 2 and 5). Increases in HR and MAP at intubation in the placebo group were 23% and 17%, respectively, in the L1 group, 15% and 11% and L2 group 11% and 9% respectively. The results found in our study are comparable with the results found by the author Amar et al. who administered 0.15 mg/kg of Inj. Labetalol for induction and 0.25–0.3 mg/kg during maintenance of anaesthesia to study effects of Inj. Labetalol in perioperative stress management. 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] The author Kim et al reported that a single dose of Inj. Labetalol (0.25 mg/kg) when administered preoperatively 5 min. before intubation decreases HR significantly after intubation up to 10 min.[17] In a study conducted by Roelofse et al, the Inj. Labetalol with the dosage of 1 mg/kg when administered a bolus dose 1 min. before laryngoscopy was not effective in the attenuation of HR. This failure of attenuating the stress response was explained by the peak effect of Inj. Labetalol seen after 5–10 min.[23] A significant difference was observed for HR between L1 and L2 group at 5 min. post-intubation (P < 0.00) indicating statistically significant. The SBP, DBP and MAP were compared between the L1 and L2 groups at intervals of 3 min., 5 min. and 10 min. post-intubation and results showed there were statistically significant different (P < 0.00). The possible explanation could be due to higher dosage which was used in group L2 when compared to group L1. As the dose was increased in group L2 the side effect observed in this group was

bradycardia intraoperatively. The bradycardia was defined when heart rate was less than 60 per min. and treated with Inj. Atropine 0.6 mg IV. Other than this there were no serious complications noted during the study after laryngoscopy and tracheal intubation in both the groups.

CONCLUSION: To conclude Inj. Labetalol in either dose 0.1 mg/kg or 0.2 mg/kg when administered IV is effective in abolishing the haemodynamic responses to direct laryngoscopy and orotracheal intubation in dose dependent manner in normotensive patients. Possibility of bradycardia should be kept in mind if the dose used is 0.2 mg/kg. A study on larger number of patients is required.

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