Effectiveness of two different doses of intravenous labetalol on attenuation of hemodynamic responses to laryngoscopy and intubation in controlled hypertensive patients undergoing major abdominal surgeries under general anaesthesia - A randomized trial

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ABSTRACT

Introduction: Laryngoscopy and endotracheal intubation provoke physiological responses, violate the patient's protective airway reflexes and predictably lead to hemodynamic changes. The present study was aimed to compare the effectiveness of two doses of intravenous labetalol in attenuating hemodynamic responses associated with laryngoscopy and endotracheal intubation by observing changes in the patient's heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). **Materials and Method**: This was a hospital-based randomized double-blinded interventional study which included 72 patients with controlled hypertension, aged between 20 to 60 years, undergoing elective open abdominal surgery, requiring general anaesthesia and orotracheal intubation. Patients were assigned into two groups of 36 each: Group A: Labetalol 0.15 mg/kg and Group B: Labetalol 0.3 mg/kg diluted with 0.9% normal saline to make up to 10 mL and was given intravenously 5 min before intubation. HR, SBP, DBP, MAP and oxygen saturation (SpO2) were recorded before induction, at the time of intubation and 1, 3, 5, and 10 min after intubation. **Results:** HR, SBP, DBP and MABP were significantly attenuated in Group B at intubation, 1 min, 3 min, 5 min, and 10 minutes after intubation**. Conclusion**: Labetalol in the dose of 0.3 mg/kg provides better hemodynamic stability than labetalol in the dose of 0.15 mg/kg on sympathetic stimulation due to direct laryngoscopy and endotracheal intubation.

Keywords: Intravenous labetalol, hemodynamic changes, direct laryngoscopy, endotracheal intubation, controlled hypertensive patients, open abdominal surgery.

INTRODUCTION

Laryngoscopy and endotracheal intubation are employed for the execution of general anaesthesia during surgery and an endotracheal tube is generally placed in the trachea to protect the airway.[1] Laryngoscopy and endotracheal intubation provoke physiological responses and stimulate patient's protective airway reflexes, leading to range of hemodynamic changes. These can result in complications ranging from mild sore throat to severe tracheal stenosis. These procedures produce an intense noxious stimulus via the vagus and glossopharyngeal nerves, resulting in reflex autonomic activation which usually manifests as hypertension and tachycardia in adults and adolescents. Manifestations due to activation of central nervous system include increased cerebral metabolic rate, cerebral blood flow and EEG activity, and a rise in intracranial pressure. These hemodynamic responses are usually of short duration. However, these may have consequences in patients with significant cardiac disease.[2] Laryngoscopy and tracheal intubation cause catecholamine release resulting in undesirable sympathomimetic effects. Various techniques have been recommended to prevent these stress responses. These include increasing the depth of anaesthesia, proper patient positioning, use of appropriate size laryngoscope blade and endotracheal tube, appropriate ETT cuff inflation, expertise of intubating the patient within 15 seconds and administration of various drugs like intravenous or topical lignocaine, intravenous opioids, beta-blockers like esmolol, alpha adrenergic agents like dexmedetomidine and clonidine, calcium channel blockers like nicardipine, verapamil, diltiazem, magnesium sulphate and other hypotensive agents like sodium nitroprusside and

nitroglycerine.[3,4] None of these agents so far have been able to limit the hemodynamic responses to laryngoscopy and tracheal intubation satisfactorily and the quest for an ideal agent continues. The present study aims to compare the effectiveness of two distinct doses of intravenous labetalol in impairing the hemodynamic responses associated with laryngoscopy and endotracheal intubation by observing changes in patient's HR, SBP, DBP and MAP. We hypothesized that there is no difference in the effectiveness of the attenuation of hemodynamic responses by the two doses of labetalol.

MATERIALS AND METHOD

This study was a hospital-based, prospective, randomized double-blind interventional study comparing two different doses of labetalol in decreasing the hemodynamic responses during direct laryngoscopy and intubation. The study was conducted at Sawai Man Singh Medical College after approval from the Institutional research review board (IEC approval No: 107/MC/EC/2020), from September 2021 to December 2021. The trial was registered prospectively as CTRI/2021/09/036263. The research was conducted in accordance with the declaration of Helsinki. 72 patients of either sex, aged 20 to 60 years, of ASA PS classes I and II who were to undergo elective open abdominal surgery requiring general anaesthesia were included in the study. According to the diagnostic criteria of the Joint National Committee on hypertension (JNC-8), hypertension was defined if systolic blood pressure >140 mm Hg and/or diastolic blood pressures were >90 mm Hg. During pre-anesthetic evaluation, patients who were hypertensive but their hypertension was controlled (blood pressure range=systolic blood pressure 140 and diastolic blood pressure 90) by antihypertensive drugs such as calcium channel antagonists (e.g., nifedipine, nicardipine, diltiazam) and renin angiotensin inhibitors (e.g.,captopril) were identified. Patients not willing to participate in the study, allergic to the study drug, those predicted with a difficult airway intubation and history of bronchospasm, cardiac disorder, severe hepatic or renal disease, pregnancy and diabetes mellitus were excluded from the study. The primary objective was to determine the variation in HR, SBP, DBP and MAP from baseline to one minute, three minutes, five minutes and ten minutes post-intubation in both groups. The secondary objective was to determine the difference in the percentage of cases who experience side effects (bradycardia, hypotension, headache, flushing etc.), if any, within 24 hours in both groups. The minimum sample size required was 72 in 2 groups of 36 patients each at 95% confidence level and 80% power to detect the difference of 3.24 (± 5.4) in MAP from baseline to 10 minutes post-intubation period between labetalol 0.15 mg/kg and labetalol 0.30 mg/kg groups.[5] This trial was planned in such a way that neither the observer nor the patients were aware of the groups or the drugs used. Both drugs were clear colourless solution of the same volume. 72 eligible patients were randomly allocated into 2 study groups by utilizing the sealed envelope method. The study was conducted in the following 2 groups of patients: Group A - injection labetalol 0.15 mg/kg i.v. as single bolus diluted into 10 cc syringe with 0.9% normal saline and administered 5 minutes before induction. Group B - injection labetalol 0.30 mg/kg i.v. as single bolus diluted into 10 cc syringe with 0.9% normal saline, administered 5 minutes before induction.

A uniform anaesthesia technique was performed for every patient. On advent into the operation theatre, nil per oral status and informed written consent were obtained for participation in the study and usage of data of patient for research and educational purposes. Pre-anaesthetic checkup was performed. Standard routine monitoring comprising of noninvasive blood pressure (NIBP), ECG, oxygen saturation (SpO_2) and baseline parameters i.e., HR, SBP, DBP, MAP and oxygen saturation (SpO_2) were noted. Peripheral intravenous cannula was secured and IV Ringer Lactate was infused at 10 mL/kg/h. Patients were premedicated with metoclopramide 10 mg i.v., glycopyrrolate 0.004 mg/kg i.v., midazolam 0.01 mg/kg i.v. and fentanyl 1 µg/kg i.v. 5 minutes before the study drug. Baseline hemodynamic parameters were recorded 5 minutes after premedication (just prior to administration of the study drug). Randomization was done using a sealed envelope method by a researcher unrelated to the study. A nurse not involved in the study prepared syringes "A" and "B". The syringes could not be distinguished from each other as they contained the same colour and volume of the injection. Envelopes were opened just before the injection and the syringes were allocated according to the group in the envelope. One researcher administered the drug and another researcher made the observations. Hence, both study patient and observer were blind to the study drugs. Group A patients received labetalol 0.15 mg/kg diluted in 10 mL saline as IV bolus and group B patients received labetalol 0.30 mg/kg diluted in 10 mL saline as IV bolus 5 minutes before induction. Induction of

anaesthesia was carried out with propofol 2 mg/kg i.v. and succinylcholine 1.5 mg/kg i.v. Intermittent positive pressure ventilation was given with 100% oxygen for 90 seconds. Hemodynamic parameters were noted before laryngoscopy. Under direct laryngoscopy, patient was intubated with an adequate sized cuffed endotracheal tube. Bilateral air entry was confirmed and tube was secured at adequate length. Hemodynamic parameters were noted at 1, 3, 5 and 10 minutes after intubation. Then, surgery was allowed to proceed and maintenance of anaesthesia was done with 50% nitrous oxide and 50% oxygen, isoflurane 1% (1 MAC), atracurium 0.5 mg/kg loading dose and 0.1 mg/kg i.v. as maintenance dose intra-operatively. On completion of surgery, neuromuscular blockade was reversed with neostigmine (0.05 mg/kg i.v.) and glycopyrrolate (0.01 mg/kg i.v.). Patient was extubated when fully awake and following verbal commands with adequate minute ventilation. Patient was kept for postoperative monitoring in the recovery room. All study patients were monitored for any adverse effects (bradycardia, hypotension, flushing, headache etc.) up to 24 h postoperatively.

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS software. Quantitative data was summarized as mean and standard deviation (S.D.) and analyzed using Student "t-test". Frequencies and percentage were analyzed using Chi square test. A "p-value"<0.05 was taken as statistically significant. Chi square test used to evaluate the difference in Sex, ASA grades and Malampatti Grades. The value of Chi square test for Sex was 0.22, for ASA Grades was 1.55 and for Malampatti Grades was 1.361.

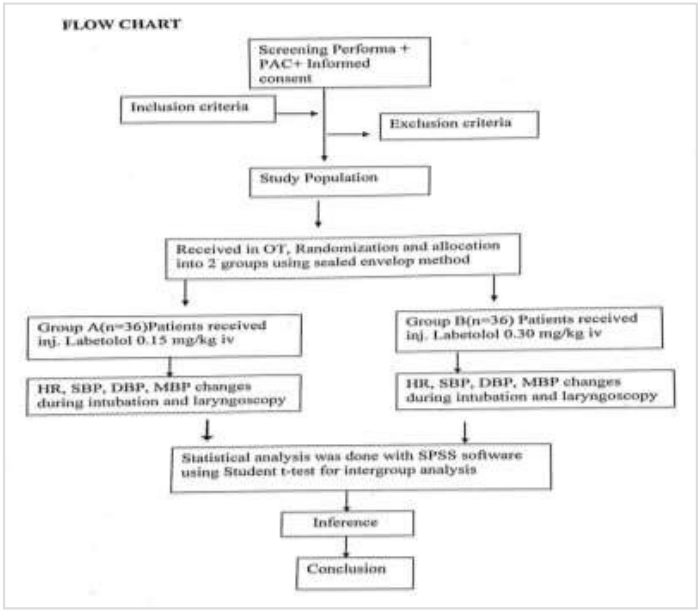

Figure 1: CONSORT Diagram

RESULTS

The study was done from September 2021 to December 2021. Both the groups were comparable with regards to age, sex, ASA PS Classification and mallampati grading (Table 1). Pre-induction readings of HR, SBP, DBP and MAP were comparable between Groups A and B with no statistically significant differences (Tables 2,3,4,5). Heart rate throughout the study time showed statistically significant difference between Group-A and Group-B (P<0.001), at intubation, 1 min, 3 min and 10 minutes post-intubation. Systolic blood pressure at intubation, 1 minute, 3 minutes, 5 minutes and 10 minutes post-intubation were significantly less in group B with a p-value less than 0.001. Diastolic blood pressure at the time intervals after administration of study drug, at intubation, 1 minute, 3

minutes, 5 minutes, and 10 minutes and post-intubation in group B were found significantly less than in group A (p-value of less than 0.001). Mean arterial blood pressures at intubation, 1 min, 3 min, 5 min and 10 min post-intubation are significantly less in group B than in group A (Tables 2, 3, 4 and 5). In the present study, patients did not experience any adverse reactions.

Table 1: Demographic and other baseline data

Parameters	Group-A(n=36)	Group-B(n=36)	p-value
Age in yrs	36.06±12.79	33.12±9.89	0.261(NS)
Sex(F/M)	17/19	20/16	0.637(NS)
ASA(I/II)	26/10	20/16	0.220(NS)
Mallampatti grade I/II/III	17/18/1	20/16/0	0.506(NS)

NS (Not significant), F (Female), M (Male), ASA (American society of Anesthesiologist)

Table-2: Heart rate (beats per minute) at different time intervals in the study groups

Time interval	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	84.42	6.64	84.89	11.80	0.834 (NS)
Before induction	80.00	7.66	82.08	11.55	0.370 (NS)
At intubation	99.33	3.30	96.42	3.58	0.0006(S)
1 min post intubation	92.94	2.65	90.89	2.78	0.001(S)
3 min post intubation	86.61	2.66	84.36	2.76	0.0007 (S)
5 min post intubation	79.31	3.27	74.08	3.71	p<0.001(S)
10 min post intubation	71.22	2.61	66.03	3.79	p<0.001 (S)

NS (Not Significant), SD (Standard Deviation), S (Significant)

Table 3: Systolic Blood Pressure (mm Hg) at different time-intervals in the study groups

Time interval	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	134.14	2.7	133.9	4.42	0.848 (NS)

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Before induction	132.36	3.00	132.75	4.04	0.644(NS)
At intubation	146.86	3.08	142.31	1.75	p<0.001(S)
1 min post intubation	136.03	2.40	131.28	2.17	p<0.001(S)
3 min post intubation	127.75	3.13	121.00	5.85	p<0.001(S)
5 min post intubation	120.67	2.24	112.86	3.89	p<0.001(S)
10 min post intubation	112.22	3.54	105.89	3.05	p<0.001(S)

NS(Not Significant) , SD (Standard Deviation), S(Significant)

Table 4: Diastolic Blood Pressure (mm Hg) at Different Time-intervals in the study groups

Time interval	Group A		Group B		p-value
	Mean	SD	Mean	SD	
Baseline	83.44	2.70	82.33	2.73	0.086 (NS)
Before induction	82.19	2.88	80.03	3.03	0.002 (S)
At intubation	94.58	2.06	91.94	2.30	p<0.001(S)
1 min post intubation	88.25	1.00	83.58	2.92	p<0.001(S)
3 min post intubation	98.53	1.48	90.94	3.23	p<0.001(S)
5 min post intubation	81.89	1.55	75.44	2.80	p<0.001(S)
10 min post intubation	72.47	1.58	68.31	2.36	p<0.001(S)

NS(Not Significant) , SD (Standard Deviation), S(Significant)

Table 5: Mean Arterial Blood Pressure (mm Hg) at Different time intervals in the study groups

Time interval	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	98.28	3.74	98.06	2.11	0.757(NS)
Before induction	95.94	3.89	98.86	2.02	0.213 (NS)
At intubation	111.39	2.16	108.17	1.42	p<0.001(S)
1 min post intubation	103.31	1.94	98.89	2.29	p<0.001(S)
3 min post intubation	107.58	1.30	100.08	2.22	p<0.001(S)
5 min post intubation	93.33	1.53	87.25	1.65	p<0.001(S)
10 min post intubation	86.83	2.12	80.64	1.82	p<0.001(S)

NS(Not Significant), SD (Standard Deviation), S(Significant)

DISCUSSION

Laryngoscopy and tracheal intubation can lead to more hemodynamic changes in hypertensive patients as compared to normotensive patients. Hypertensive patients can develop an array of complications including pulmonary oedema, heart failure and cerebrovascular accident following hypertensive episodes which can be a direct effect of tracheal intubation. In healthy individuals, there are transitory increases in BP and HR, but these fluctuations can be more harmful to those with hypertension, heart failure or cerebrovascular diseases. Therefore, in hypertensive patients, the attenuation of hemodynamic responses following laryngoscopy and endotracheal intubation is of significant consequences.

Within one minute of laryngoscopy and tracheal intubation, maximum hemodynamic response occurs. Therefore, drug administration to attenuate response should be timed in such a way that the peak effect corresponds to the timing of hemodynamic response, which is between 5 to 15 min for Labetalol, and times well with the laryngoscopy and intubation response.[6] We recorded the hemodynamic response to laryngoscopy and intubation for 10 min as this is the average duration to which hemodynamic fluctuations to direct laryngoscopy and intubation lasts. The hemodynamic responses and catecholamine release during laryngoscopy should be distinguished from effects seen at the time of endotracheal intubation.

In the current study, the effectiveness of two different doses of i.v. Labetalol in attenuation of hemodynamic responses (HR, SBP, DBP, MAP) to direct laryngoscopy and endotracheal intubation in controlled hypertensive patients under general anaesthesia in major abdominal surgeries was compared. The primary objective was to determine the difference in variation in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure from baseline to 1 min, 3 min, 5 min, and 10 min post-intubation in both groups. The secondary objective was to determine the difference in the percentage of cases who experience side effects (Bradycardia, hypotension, headache and flushing etc), if any, within 24 hours in both groups.

Demographic characteristics of the sample population were similar between the study groups. On statistical analysis, mean age and sex distribution in group A and B were comparable. Patient in our study were either ASA physical status classes I and II without statistical difference in their distribution between the study groups (Table-1). Similar results obtained by Khan et al[7], who showed that age, gender and ASA physical status were comparable in between groups and there was no

statistical difference in between them. Also, pre-induction readings of heart rate (HR), SBP, DBP and MABP were comparable between both groups.

Heart Rate

Statistically significant difference was seen in entirety of study time between Group A and Group B at the time of intubation, 1 minute, 3 minutes, 5 minutes and 10 minutes post-intubation. This was due to usage of higher dose of labetalol in group B (0.3 mg/kg) as compared to Group A (0.15 mg/kg). These results are consistent with the findings ofLeslie et al[8] who reported dose-dependent attenuation of the rise in heart rate following i.v. labetalol at doses up to 0.75 mg/kg. Kim et al[9] recorded that bolus of labetalol 0.25 mg/ kg given 5 minutes before intubation decreased HR significantly up to 10 min after intubation. Khan et al[7]showed that labetalol 200 mg single oral dose administered 60-90 min prior to direct laryngoscopy was not effective in the subsidence of HR. They demonstrated that oral labetalol showed minimum control of heart rate. These differing findings in these studies can be justified by the difference in the time of administration of the study drug as labetalol has a peak effect after 5–10 min.

Systolic Blood Pressure

The present study showed that intravenous injection of labetalol in two distinct doses attenuates the increase in systolic blood pressure after direct laryngoscopy and tracheal intubation in a dose-dependent manner. Statistically significant difference was seen in SBP between Group A and Group B at intubation, 1 minute, 3 minutes, 5 minutes and 10 minutes post-intubation ($P < 0.001$) with better attenuation seen in Group B. Similar results were obtained by Kaladhar et al.[10]They compared the attenuation of hemodynamic changes between i.v. lignocaine and i.v. labetalol in laryngoscopy and endotracheal intubation. They showed more significant attenuation of systolic blood pressure with labetolol as compared with lignocaine. Ambasta et al[11]showed systolic blood pressure between two groups remained same before intubation but at intubation and 1, 3, 5 and 10 min following intubation; results were in favor of labetalol group which had lower values as compared to the esmolol group. Kumar et al.[12] showed that systolic blood pressure showed a statistically significant difference at different intervals. They compared the efficacy of esmolol and labetalol for attenuation of sympathomimetic response to laryngoscopy and intubation in 75 adult patients with ASA 1 and ASA 2 posted for elective surgeries. Patients were allocated randomly into Group-1 (esmolol) and Group-2 (labetalol) and Group-3 (placebo) of 25 patients each. Inj. esmolol (1 mg/kg) or Inj. labetalol (0.4 mg/kg) or placebo (0.9% NS) dissolved up to 5 ml in distilled water was injected intravenously 5 minutes prior to intubation. Haemodynamic readings were noted at T0 (baseline before injecting the drug), T1 (1 minute after injecting the drug), T2 (after intubation), T3 (2 minutes after intubation), T4 (4 minutes after intubation), T5 (6 minutes after intubation), T6 (8 minutes after injection), T7 (10 minutes after injection). These three groups were compared for mean SBP (systolic blood pressure) at different time intervals. This study showed that Group 1 and 2 shows significant difference ($p<.001$) in mean SBP just after intubation to 10 minutes time interval after intubation. Group 2 and 3 also shows statistically significant difference ($p<.001$) in mean SBP from just after intubation to 10 minutes after intubation time interval.

Diastolic Blood Pressure

The present study showed attenuation of DBP in both groups with statistically significant difference between Group A and Group B immediately after the drug administration, immediately prior to intubation, 1 minute, 3 minutes, 5 minutes and 10 minutes after intubation with greater attenuation in an increase in diastolic blood pressure in Group B. Therefore, labetalol attenuates hemodynamic responses in a dose-dependent manner. Our study result aligned with those of Leslie et al[7] who showed dose-dependent inhibition of increases in systolic, diastolic and mean blood pressures versus placebo post intubation. I.V. labetalol at doses up to 0.75 mg/kg acts as an effective pharmacologic method of decreasing preoperative hemodynamic responses to endotracheal intubation.

Mean Arterial Blood Pressure

MABP in Group A as compared to Group B was significantly higher at the time of intubation and also at 1 minute, 3 minutes, 5 minutes and 10 minutes post-intubation. The present study showed that the i.v. administration of labetalol in two different doses attenuates the increase in MABP after direct laryngoscopy and tracheal intubation. Our results are comparable with the findings of Sangeetha et al.[13]who showed reduction in the heart rate and mean arterial pressure response to intubation in both dexmedetomidine and labetalol groups compared with placebo ($P< 0.05$). Kim et al[8] reported that

bolus dose of labetalol 0.25 mg/kg given preoperatively 5 min before intubation decreased HR and MABP significantly after intubation up to 10 min.

Adverse reactions

In the present study, patients did not experience any adverse reactions like bradycardia, hypotension, headache, flushing, nausea etc. Perhaps, this was attributed to the fact that we used low doses of labetalol (0.15mg/kg and 0.3 mg/kg).

Limitations: The limitations of the study were the small sample size. Thus, the inference can not be applied to a larger population. Further studies would be required to corroborate the finding.

CONCLUSION

Labetalol in the dose of 0.3 mg/kg provides better hemodynamic control than labetalol in the dose of 0.15 mg/kg against the increase in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure associated with direct laryngoscopy and tracheal intubation in patients with controlled hypertension. Labetalol in these doses does not produce any adverse reactions. Further studies are required to substantiate these findings.

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