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Original Article

Anaesthesia Section

Intravenous Labetalol vs Intravenous Clonidine for Attenuation of Haemodynamic Responses during Laryngoscopy and Intubation in Controlled Hypertensive Patients Undergoing General Anaesthesia- A Randomised Clinical Trial

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ABSTRACT

Introduction: Laryngoscopy and endotracheal intubation during general anaesthesia are associated with haemodynamic surges which can be detrimental, particularly if there is pre-existing hypertension or cardiovascular disease. Intravenous (i.v.) labetalol, a β-adrenergic blocker with additional α1-adrenoceptor blocking activity, and clonidine, a centrally acting α2 agonist, are known to attenuate this haemodynamic response.

Aim: To compare the effects of i.v. labetalol and clonidine in attenuating haemodynamic changes during laryngoscopy and intubation in controlled hypertensive patients.

Materials and Methods: This single centre, parallel-group, double-blind, randomised clinical trial was conducted in the Surgery Operation Theatre (OT) of Midnapore Medical College, District Paschim Medinipur, West Bengal, India, from February 2018 to August 2019. The study included 90 adult patients of either sex, who were randomly allocated to receive either clonidine 1 mcg/kg or labetalol 0.15 mg/kg by intravenous route. After recording baseline parameters, patients were preoxygenated with 100% oxygen for 3 min and the study drug was given 5 min prior to induction. Heart Rate (HR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and the rate pressure product were recorded prior to induction, at the time of intubation and 1, 3, 5, and 10 min after intubation. General anaesthesia maintenance was done in a similar manner in both groups. Two-sample t-test was used to assess significance of difference in means between independent samples. Fischer's-exact test was employed for comparing categorical data. Analysis was two-tailed and p-value <0.05 was considered statistically significant.

Results: Both the groups were evenly matched at baseline with respect to age and sex as well as standard anthropometric parameters (p-value >0.05). Both drugs were able to attenuate the expected rise in HR following intubation but labetalol was more effective than clonidine throughout the postintubation period. SBP and DBP were comparable between the two groups at baseline but underwent greater attenuation in the labetalol group at intubation and subsequent measurements. The differences were around 10 bpm for HR, 20-30 mmHg for SBP and 10 mmHg for DBP, in favour of labetalol. Adverse events like bradycardia, hypotension, sedation or undesirable ECG changes were not encountered.

Conclusion: Intravenous labetalol is more effective than i.v. clonidine in controlling haemodynamic changes during laryngoscopy and intubation in controlled hypertensive patients undergoing general anaesthesia without any complications.

Keywords: Diastolic blood pressure, Heart rate, Haemodynamic surge, Systolic blood pressure

INTRODUCTION

Laryngoscopy and endotracheal intubation are integral part of General Anaesthesia (GA). These procedures are associated with reflex sympathetic stimulation, manifesting as undesirable surges in heart rate and blood pressure. Triggered by the reflex changes in the autonomic and cardiovascular systems, there is rise in Blood Pressure (BP) by average 20-40% and in Heart Rate (HR) by average 20% [1]. Many pharmacological agents like beta-blockers, opioids, nitroglycerine, sodium nitroprusside, calcium channel blockers, volatile inhalational agents, intravenous (i.v.) lignocaine, etc., have been used in attempt to attenuate this undesirable pressor response [2].

Labetalol is a unique oral and parenteral antihypertensive drug which is selectively antagonistic for α1, β1 and β2-adrenergic receptors. It has been used for attenuation of haemodynamic response to laryngoscopy and intubation [3,4]. Clonidine, a centrally acting α2 agonist, introduced for treatment of hypertension, decreases intraoperative anaesthetic and analgesic requirement. It is also effective in attenuation of laryngoscopy induced haemodynamic surges [5,6].

There are multiple studies on intravenous clonidine and labetalol individually, and in comparison, with other drugs and most have observed significant attenuation of haemodynamic changes during general anaesthesia [3-6]. However, there is no direct comparison between i.v. labetalol and i.v. clonidine in the attenuation of laryngoscopy and intubation associated haemodynamic surge in patients who are known to be hypertensive but controlled on medication. There is only one comparative study between oral clonidine and labetalol in this context, in which the authors concluded that oral clonidine showed better attenuation of haemodynamic changes than oral labetalol [7].

With this background, this study aimed for a head-to-head comparison of the performance of these two agents administered i.v. in the doses 0.15 mg/kg (labetalol) and 1 mcg/kg (clonidine). The primary outcome measure was HR measured at laryngoscopy-intubation

and at 1, 3, 5 and 10 minutes thereafter. The secondary outcomes were changes in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and Rate Pressure Product (RPP) measured at the same time points.

MATERIALS AND METHODS

This single centre, parallel-group, double-blind, randomised clinical trial was conducted in the Surgery Operation Theatre (OT) of Midnapore Medical College, District Paschim Medinipur, West Bengal, India, from February 2018 to August 2019. It is a tertiary care referral hospital catering to a predominantly rural catchment area. The study conformed to the Declaration of Helsinki and the Indian Council of Medical Research (ICMR) guidelines for Biomedical Research Ethics and received due approval from the Institutional Ethics Committee (MMC/IEC-2-2017/2623 dated 13.12.2017). Written informed consent was obtained from all participating subjects.

Inclusion criteria: Hypertensive patients of either sex, aged between 18-65 years and controlled on medication (office BP in seated position at 140/90 mmHg or below) were included. Patients were on one or more first line antihypertensives {from among calcium channel blockers, Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARBs)} and were posted to undergo elective laparoscopic cholecystectomy under general anaesthesia.

Exclusion criteria: Patients with anticipated difficult intubation, heart rate <60 bpm, history of ischaemic heart disease, on β-blockers or other medication for cardiovascular disease were excluded from the study. Patients with secondary hypertension and significant co-morbidity (e.g. uncontrolled diabetes mellitus, chronic obstructive pulmonary disease, thyroid disorders) were also not included. Finally, during the procedure, patients requiring more than 15 seconds for laryngoscopy and intubation were excluded from the study.

Sample size calculation: A pilot study was conducted taking 10 controlled hypertensive patients undergoing laparoscopic cholecystectomy. Heart rate change was taken as the primary outcome and a difference of 10 bpm between the two groups was taken as clinically meaningful to reject the null hypothesis. The standard deviation encountered was 14 mmHg. Taking the Type I error probability to be 5%, power of the study to be 90%, two-sided testing and balanced allocation, it was calculated that 41 patients were required in each of the two study groups. However, keeping 10% margin to counter dropouts, it was decided to recruit 45 patients in each group.

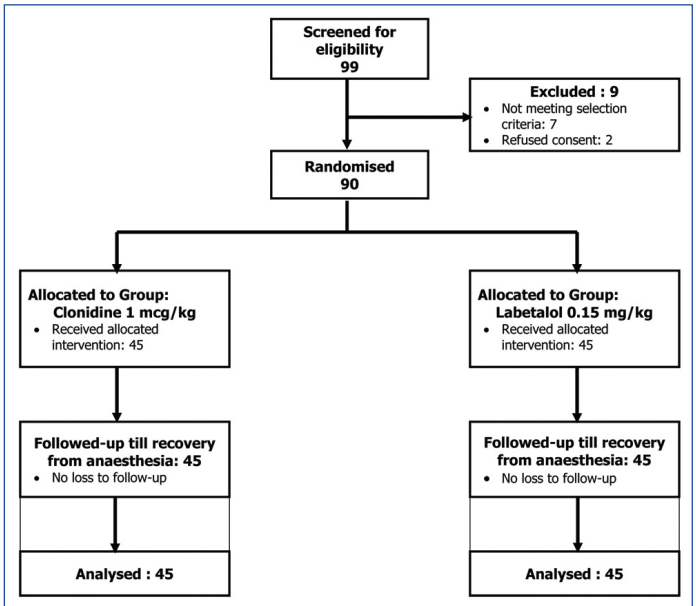
Sampling for the study was purposive in nature. Randomisation was done by computer generated random numbers using the WinPepi (version 11.61, J. H. Abramson; 2016) software. Allocation was concealed by serially numbered opaque sealed envelope technique, till recruitment of a subject was confirmed and a resident, not participating in the study, opened the allocated envelope in the OT and prepared the injection syringe without the knowledge of the investigator who administered the drug and monitored the patient.

- Clonidine group (n=45): Patients received i.v. clonidine 1 mcg/kg.
- Labetalol group (n=45): Patients received i.v. labetalol 0.15 mg/kg.

The injection volume was made upto 5 mL in every case by normal saline. Thus, both patient and investigator remained blind. There were no dropouts in this study and all 45 subjects in each group were included in the effectiveness evaluation, obviating the need for any intention-to-treat analysis. [Table/Fig-1] presents a Consolidated Standard for Reporting Trials (CONSORT) style flow diagram for the study.

Study Procedure

Patients were kept nil orally for eight hours before surgery and the regular hypertensive medication of the patient was given at 6 AM on the day of surgery to control the blood pressure. Then each patient



[Table/Fig-1]: Flowchart showing patient disposal in the study.

was given premedication with injection (Inj) ondansetron 0.1 mg/kg and Inj midazolam 0.05 mg/kg 10 min before induction.

Then baseline parameters were recorded and the study drug was given intravenously 5 min prior to induction over a period of 30 seconds. Patients were preoxygenated with 100% oxygen by a facemask for 3 min. Then induction was done by thiopentone sodium 5 mg/kg i.v. and, with the loss of eyelash reflex, vecuronium 0.1 mg/kg i.v. was given. After 3 min of mask ventilation, direct laryngoscopy was done with proper size Macintosh laryngoscope blade. Trachea was intubated with proper size cuffed Polyvinyl Chloride (PVC) endotracheal tube. None of the patients received opioids and topical lidocaine before laryngoscopy. All intubations were performed and accomplished within 15 seconds by experienced anaesthesiologist with more than seven years of experience, although the same person did not intubate all patients in the study. After intubation, anaesthesia was maintained by 66% nitrous oxide, 33% oxygen and 1% isoflurane, with intermittent boluses of 1mg vecuronium bromide as required. HR, SBP, DBP and RPP were recorded prior to induction, at the time of intubation and 1, 3, 5, and 10 min after intubation. Abnormal Electrocardiogram (ECG) changes and adverse events like hypotension, bradycardia, and sedation were recorded. Inj. fentanyl 2 mcg/kg was given at 10 min after intubation and repeated hourly. Additionally, paracetamol infusion 15 mg/kg was administered intraoperatively for analgesia. End-tidal carbon dioxide was maintained between 30-40 mmHg. At the end of surgery, effect of muscle relaxant was reversed by Inj. neostigmine 50 mcg/kg and Inj. glycopyrrolate 10 mcg/kg.

STATISTICAL ANALYSIS

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by Statistical version 8 [Tulsa, Oklahoma: StatSoft Inc., 2007] and GraphPad Prism version 5 [San Diego, California; GraphPad Software Inc., 2007] software. Data have been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-test was used to assess significance of difference in means between independent samples. Fischer's-exact test was employed for comparing categorical data. Analysis was two-tailed and p-value <0.05 was considered statistically significant.

RESULTS

As seen from [Table/Fig-2], the groups were evenly matched at baseline with respect to age and sex as well as standard anthropometric parameters.

Variables	Clonidine (n=45)	Labetalol (n=45)	p-value
Age (year)	48.8±8.89	47.6±7.72	0.47
Gender (Male/Female)	23/22	18/27	0.40
Height (metre)	1.62±0.09	1.60±0.08	0.22
Weight (kg)	58.6±8.5	57.1±7.9	0.38
Body mass index (kg/m^2)	22.2±1.35	22.3±1.42	0.87

[Table/Fig-2]: Demographic and anthropometric profile compared between the two study groups.

[Table/Fig-3] summarises the sequential haemodynamic changes attending laryngoscopy and intubation in the two study groups, in terms of HR, SBP, DBP and RPP. Heart rate was significantly higher in the labetalol group prior to induction and at the time of intubation. However, following intubation it attenuated rise in heart rate better than clonidine at all the subsequent time points. SBP and DBP were comparable between the two groups at baseline but underwent greater attenuation in the labetalol group at intubation and at all subsequent measurements. The differences were around 10 bpm for heart rate, 20-30 mmHg for SBP and 10 mmHg for DBP, in favour of labetalol. The RPP reflected a similar pattern of greater attenuation with labetalol following intubation.

Parameters	Clonidine group (Mean±SD)	Labetalol group (Mean±SD)	p-value
Heart rate (bpm)			
Prior to induction	78.5±7.62	85.7±6.25	<0.001
At time of intubation	85.3±7.06	89.8±6.19	0.002
1 min after intubation	145.2±5.44	128.7±4.97	<0.001
3 min after intubation	137.6±5.13	122.2±4.07	<0.001
5 min after intubation	130.8±4.86	114.9±5.41	<0.001
10 min after intubation	125.4±4.68	104.9±6.26	<0.001
Systolic blood pressure (mmHg)			
Prior to induction	125.6±4.64	127.2±4.81	0.103
At time of intubation	135.2±4.55	132.5±5.51	0.011
1 min after intubation	174.7±6.86	146.0±6.72	<0.001
3 min after intubation	164.6±8.13	135.0±6.96	<0.001
5 min after intubation	154.3±7.97	128.8±4.63	<0.001
10 min after intubation	142.0±6.45	123.9±3.52	<0.001
Diastolic blood pressure (mmHg)			
Prior to induction	81.1±3.96	81.7±3.59	0.437
At time of intubation	87.4±3.78	85.2±3.44	0.005
1 min after intubation	101.1±2.91	93.7±2.28	<0.001
3 min after intubation	98.9±3.15	89.7±2.89	<0.001
5 min after intubation	96.0±3.40	86.8±3.65	<0.001
10 min after intubation	91.9±4.13	83.4±3.23	<0.001
Rate pressure product (Units)			
Prior to induction	9872.5±1182.55	10910.4±1002.11	<0.001
At time of intubation	11555.5±1186.18	11899.3±1060.61	0.151
1 min after intubation	25362.4±1419.73	18791.8±1123.63	<0.001
3 min after intubation	22661.0±1521.64	16510.2±1071.39	<0.001
5 min after intubation	20187.8±1448.93	14802.0±979.08	<0.001
10 min after intubation	17822.0±1275.92	13009.9±897.34	<0.001

[Table/Fig-3]: Haemodynamic changes during laryngoscopy and intubation compared between the two study groups.

No clinically significant adverse events like hypotension, bradycardia, bronchospasm, arrhythmias or ischaemic changes on ECG were found in any of the groups. Thus, addition of neither clonidine nor labetalol, in the doses used, adversely affected the safety profile of the GA regimen.

DISCUSSION

Laryngoscopy and intubation stimulate the patient's airway leading to sympatheticoadrenal excitation, manifesting as sharp rise in HR, blood pressure and plasma catecholamine concentrations. Usually, these changes are tolerated well by healthy persons but may cause complications such as myocardial ischaemia, ventricular arrhythmia, left ventricular failure, and cerebral haemorrhage, in patients with pre-existing hypertension [8]. The magnitude of cardiovascular response to laryngoscopy and intubation may vary with duration and difficulties encountered during the procedure as well as patient dependent variables like age, cardiovascular diseases, diabetes and other co-morbidities. Hypertensive patients are at increased risk of pulmonary edema, myocardial ischaemia, infarction and cerebrovascular accidents. Therefore, it is suggested that rapid correction of BP or prevention of rise in heart rate may be all that is needed to reduce perioperative risks associated with hypertension [9].

It is previously reported that the beta-blocker labetalol can prevent undesirable perioperative cardiovascular events without undue risk of hypotension and bradycardia. Labetalol reaches its peak effect at 5-15 min after i.v. injection and rapidly redistributes. It lowers BP by decreasing systemic vascular resistance through selective α1 blockade, while reflex tachycardia triggered by vasodilatation is attenuated by simultaneous β1 and β2 blockade but cardiac output remains unchanged [10]. In a previous study where attenuation of haemodynamic responses to laryngoscopy and intubation with two different doses of labetalol was compared in hypertensive patients, doses of 0.15 mg/kg and 0.30 mg/kg both significantly reduced intubation surge compared to placebo but there was not much difference between the two doses [11]. Since escalating doses are likely to invite hypotension and bradycardia, the 0.15 mg/kg dose was selected for this study.

The centrally acting α2-adrenoceptor agonist clonidine attenuates noradrenaline release in the central nervous system and thereby reduces central sympathetic outflow. Clonidine is clinically useful due to its sympatholytic, analgesic, sedative and anxiolytic effects without causing respiratory depression [12]. The onset of action is within 3 min and peak effect occurs in about 30 min upon i.v. infusion in hypertensive patients [13]. In one study, where i.v. clonidine was used for attenuation of haemodynamic response to laryngoscopy and orotracheal intubation in doses of 1 and 2 mcg/kg, both doses were successful but the higher dose was associated with more postoperative hypotension and sedation [6]. Therefore, the lower effective dose of 1 mcg/kg was selected.

In the present study, labetalol was found to be more effective in attenuating haemodynamic variables compared to clonidine throughout the study period. Previous studies with labetalol have also reported it to be effective, although direct comparisons with clonidine in controlled hypertensive patients are not available. Singh SP et al., observed labetalol was superior to esmolol in attenuating tachycardia at all points in their study [3]. Ekambaram K and Venkatraman V, and Kumar R et al., have also reported similar findings [4,11]. However, Laxmi S et al., observed no significant difference in terms of HR control between the two during laryngoscopy and intubation [14]. However, both drugs were more effective compared to placebo.

Some older studies also strike a discordant note. For instance, Roelofse JA et al., found that labetalol 1 mg/kg given as an i.v. bolus one min before laryngoscopy was not effective in attenuation of HR [15]. This discordance may be explained by the fact that labetalol has peak effect after 5-10 min, and the 1 min interval may have been too short to notice the drug's effects. Few other older studies have also reported labetalol to be ineffective or less effective in attenuating blood pressure surges but the drug administration timings have not been clearly mentioned [16,17].

Regarding clonidine, different findings have been reported when used for attenuation of laryngoscopy and intubation associated haemodynamic surge. Sameenakausar et al., observed 2 mcg/kg clonidine is more effective than fentanyl in attenuation of sympathetic

response to laryngoscopy and intubation [5]. Arora S et al., reported that both 1 mcg/kg and 2 mcg/kg clonidine are equally effective in preventing haemodynamic surge during laryngoscopy and intubation [6]. Mondal S et al., in a study on adult patients who were pretreated with either dexmedetomidine 1 mcg/kg or clonidine 2 mcg/kg concluded that clonidine was less effective than dexmedetomidine in attenuating the stress response to intubation [18]. However, Sarkar A et al., compared clonidine 3 mcg/kg and dexmedetomidine 0.5 mcg/kg and concluded that both drugs were effective in reducing the sympathetic response to intubation [19].

Limitation(s)

This was a single-centre study, but all intubation procedures were not done by the same anaesthesiologist. The effective observation period was limited to 10 min following laryngoscopy and intubation. The serum levels of stress markers such as cortisol and catecholamines were not evaluated. Finally, preselected doses were used which raises the possibility that perhaps a higher dose of clonidine would have compared better against labetalol, without significant complications.

CONCLUSION(S)

Despite these limitations, intravenous labetalol, in a dose of 0.15 mg/kg, can satisfactorily attenuate the expected haemodynamic surge during laryngoscopy and endotracheal intubation in controlled hypertensive patients undergoing general anaesthesia. The drug is well tolerated at this dose and performs better than clonidine in this regard. Future studies may be planned with intravenous labetalol in higher doses and in laparoscopic surgery under general anaesthesia.

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