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Original Research Article

To Compare the Efficacy of Intravenous Esmolol and Diltiazem for Attenuating Hemodynamic Pressor Response to Laryngoscopy Intubation and Pneumoperitoneum in Laparoscopic Cholecystectomy

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Conflict of interest: Nil

Abstract

Introduction: Laryngoscopy and pneumoperitoneum during intra-operative period under general anaesthesia causes hemodynamic variation. So, we decided to compare the effect of esmolol and diltiazem so as to decrease the pressor response.

Methodology: 150 patients were equally divided into 3 groups i.e. Group E, Group D, Group C, and injection esmolol and diltiazem were given before intubation and creation of pneumo peritoneum, with last group as taken as control. We observed the hemodynamic variation in patients during intra-operative period and record them.

Result: We observed that heart rate and blood pressure variation was comparatively less in group E and D, as compare to group C after laryngoscopy and creation of pneumoperitoneum, whose duration was seen for few minutes and then it became same as Group C.

Conclusion: We concluded that Injection Esmolol and Diltiazem causes less hemodynamic variation after laryngoscopy and creation of pneumoperitoneum.

Keywords: Laryngoscopy, Peumoperitoneum, Esmolol, Diltiazem.

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Introduction

Laryngoscopy in anaesthesia is used to facilitate endotracheal intubation for the purpose of delivery of oxygen, inhalational anaesthetic agents and mechanical ventilation. Endotracheal intubation has thus become an integral part in general anaesthesia & management of critically ill patients. Direct laryngoscopy and endotracheal intubation following induction is invariably associated with adverse stress response [1]. The hemodynamic response is due to reflex sympathetic discharge caused by epi-pharyngeal and laryngo-pharyngeal stimulation that leads to increase in plasma epinephrine and norepinephrine, which in turn leads to increase in heart rate and blood pressure.

Tachycardia and hypertension following laryngoscopy and tracheal intubation are generally short lived, variable and unpredictable. This may also manifest as increased myocardial oxygen demand and arrhythmia. They may have detrimental effect in high risk patients especially those with cardiovascular disease, increased intracranial pressure or with anomalies of cerebral vessels [2]. Laparoscopic surgeries are replacing a variety of open procedures because they are relatively non-invasive, which means small incision, fast recovery, and less pain. However, they are associated with marked hemodynamic changes mainly due to creation of pneumo-peritoneum. Pneumo-peritoneum with carbon dioxide (CO2) for laparoscopic surgery induces a rapid increase in arterial pressure, systemic vascular resistance, central venous pressure and heart rate [3,4]. This hemodynamic stress response leads to increased myocardial oxygen demand, deleterious to patients with compromised cardiac function [5,6]. The procedure of laryngoscopy and intubation not only confined to operating room but also used in many non-anaesthetic procedures like, diagnostic laryngoscopy, fiberoptic bronchoscopy, for prevention of aspiration, protection of airway

and mechanical ventilation which may provoke sympathetic response making patients vulnerable to its side effects.

Various drugs and techniques have been used in the past from time to time to attenuate this hemodynamic response. Stress response can be prevented by increasing the depth of anaesthesia, limiting the duration of laryngoscopy to <15 seconds, and the use of various pharmacological agents such as intravenous and topical lignocaine, fentanyl, beta-blockers such as Labetalol, Calcium channel blockers such as Verapamil, Diltiazem, and Nicardipine, and other agents such as Magnesium sulphate, Nitroprusside, and Nitroglycerine[7,8,9]. No single drug or technique has found to be completely satisfactory. Large doses of fentanyl causes bradycardia, nausea and vomiting. IV lignocaine is less effective and magnesium sulphate does not prevent pressor response, clonidine attenuates pressor response but associated with post-operative sedation [10,11].

Esmolol is an ultra-short-acting intravenous cardio selective beta-antagonist. Onset of activity occurs within 2 minutes, it has extremely short elimination half-life of 9 minutes, and with principal adverse effect of esmolol is hypotension and diaphoresis [12]. Diltiazem is a benzothiazepine derivative calcium channel blocker with antihypertensive and vasodilating properties. It primarily works by inhibiting the calcium influx into cardiac and vascular smooth muscle during depolarization. It has elimination half-life of 4 hr [13]. Still choice for the ideal agent in controlling stress response is going on. So in our study, we aim at evaluating the efficacy of intravenous Esmolol and Diltiazem for attenuating stress response due to Laryngoscopy, Intubation and Pneumo-peritoneum.

Methodology

The study was conducted after obtaining hospital Ethics committee approval. Written and informed consent were taken from the patients in Department of Anaesthesia and Critical Care, Hindu Rao Hospital and associated North Delhi Municipal Corporation Medical College, Delhi. Our study was Prospective, Interventional, Randomized, Comparative, Double Blind Study, which was conducted on 150 patients who were scheduled for elective surgery under general anaesthesia over the period of 18 months from August 2019 to February 2021.

The patients were randomly allocated into 3 groups of 50 each to receive the test drug, i.e., Group D: IV Diltiazem (0.2 mg/kg), Group E: IV Esmolol (1.5 mg/kg), and Group C: Control group receiving 10 ml of normal saline. Another anaesthesiologist who were not involved in the study diluted the test drug to a volume of 10 ml in an un-labeled sterile syringe. Patient assessment and observations were recorded by the second author who was unaware of the test drug being administered. Computerized randomization technique were used for allocation of patient to particular group. Inclusion criteria for our study was Patients between 18-60 years of age, who came under ASA classification of grade I and grade II, and scheduled for elective laparoscopic cholecystectomy under general anaesthesia. Exclusion criteria for our study was

Patients with coexisting cardio-respiratory illness, significant gastrointestinal, respiratory, neurological, renal or endocrine disease, contraindication for beta blocker or calcium channel blocker, with anticipated difficult airway or who required more than one attempt for intubation / prolonged laryngoscopy (>15s). Patients with history of allergic reaction to any of the drugs used in this study, or on antihypertensive medications and obese patients.

After complete PAC, i.e. detailed history, complete physical examination and routine investigations were checked, the anaesthetic procedure were explained to the patient. All patients were asked to fast overnight for 8hours & they all should receive tablet Alprazolam 0.5 mg orally the night before surgery. In the operating room, all patients were monitored by using standardized anaesthesia techniques as Electrocardiogram, non-invasive blood pressure, pulse oximetry, and capnography. Two intravenous access with 18G/20G was secured and a crystalloid IV infusion was started. After pre-oxygenation for 3 minutes with 100% oxygen, patient were induced with intravenous fentanyl 2 mcg/kg IV, intravenous propofol 1-2mg/kg IV titrated to the loss of verbal response, and Vecuronium 0.1 mg/kg. After muscle relaxant, test drug either esmolol 1.5 mg/kg or diltiazem 0.2 mg/kg were given iv bolus (in 10 ml normal saline) and 2 min after that patient were intubated with an appropriately sized cuffed, oro-tracheal tube under direct laryngoscopy. Anaesthesia was maintained with O2 and N2O, Isoflurane (MAC:1) and Vecuronium 0.02mg/kg intermittently. At the end of surgery, diclofenac 75 mg iv, and ondansetron 4 mg iv was administered. After the procedure, patient was reversed using Inj. Neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg). Patient were extubated after proper oropharyngeal suctioning and return of airway reflex with adequate reversal of muscle power. Parameters which were measured in our study are Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, End tidal CO2, Oxygen saturation, on different time intervals i.e. Before giving study drug (baseline recording), Before induction, Immediately after intubation, 1 minute after intubation, 3 minutes after intubation, 5 minutes after intubation, 10 minutes after

intubation/ before pneumoperitoneum, 10 minutes after pneumoperitoneum, 15 minutes after pneumoperitoneum, 20 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum. Incidence of all the parameters was recorded in both the groups and decision to give appropriate therapies were taken.

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Categorical variables were analysed using either the chi square test or Fisher's exact test.

One-way analysis of variance (ANOVA) was used to evaluate the significance of the differences among three groups. If the F value was significant and variance was homogeneous, Tukey's multiple comparison test was used to assess the differences between the individual groups; otherwise, Tamhane's T2 test was used. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

Result

The mean age in Group C (control) was found to be 34.30 ± 8.46, in Group D it was 33.26 ± 7.53 and in Group E it was 35.70 ± 9.86 which were comparable with each other with p value of 0.371, which was not significant. In Group C there were 60% ASA grade I patients and 40% grade II patients, in Group D there were 68% ASA grade I and 32% grade II patients, and in Group E 52% ASA grade I and 48% grade II patients with p value of 0.264, which was statistically insignificant. The mean BMI in Group C was 24.05±4.04, in Group D was 24.12±3.61 and in Group E was 24.13±3.18 which were comparable with each other. There was statistically insignificant difference in BMI between the study groups with p value of 0.992. The mean duration of surgery (in minutes) in Group C was 64.4±9.24, in Group D was 63.3±9.93 and in Group E was 66.5±9.44 which was statistically insignificant with p value of 0.720.

Table 1: Comparison of heart rate at different time intervals between 3 groups

	Group C	p-value	Group D	p-value	Group E	p-value
T1	97.48 ± 8.58		98.28 ± 8.37		97.42 ± 6.51	
T2	97.8 ± 8.64	0.479	97.84 ± 8.66	0.318	97.34 ± 6.28	0.817
T3	100.24 ± 8.16	<0.001	98.56 ± 8.04	0.437	96.68 ± 5.93	0.124
T4	102.8 ± 8.13	<0.001	99.32 ± 7.93	0.144	92.60 ± 7.22	<0.001
T5	107.68 ± 8.7	<0.001	95.08 ± 8.08	<0.001	90.56 ± 7.64	<0.001
T6	106.8 ± 8.24	<0.001	95.48 ± 7.12	<0.001	89.02 ± 7.3	<0.001
T7	105.88 ± 8.71	<0.001	94.60 ± 7.7	<0.001	86.96 ± 8.93	<0.001
T8	104.8 ± 8.4	<0.001	93.76 ± 7.44	<0.001	85.48 ± 9.38	<0.001
T9	103.94 ± 9.1	<0.001	92.58 ± 8.26	<0.001	84.38 ± 9.34	<0.001
T10	98.4 ± 7.97	0.405	98.26 ± 7.59	0.985	96.28 ± 8.47	0.567
T11	97.44 ± 7.2	0.970	98.94 ± 7.38	0.521	95.80 ± 7.95	0.248

The baseline heart rate was comparable among the three groups and there was statistically insignificant difference between them at zero time interval.

On comparison of group C with group D at different time intervals on the basis of heart rate there was sudden increase in heart rate in group C which was not seen in group D after the injection of Injection diltiazem, so there was a statistically significant difference was present with a p-value of less than 0.05. On comparison of group C with group E at different time intervals on the basis of heart rate, same scenario was seen (after the injection of Esmolol in group E) with p value less than 0.05.

On comparison of group D with group E at different time intervals on the basis of heart rate, group E has better heart rate control with a p-value of less than 0.05. So, group E has minimum changes in heart rate at different time intervals among 3 groups.

On comparing all the 3 groups on the basis of mean blood pressure at different time intervals p value was insignificant during initial time intervals but it become significant after the injection of injection diltiazem and injection esmolol. P-value was significant between the group C and group D and group E. In control group, no adverse effect was seen. In diltiazem group two patients developed hypotension and one developed bradycardia while in esmolol group two patients developed bradycardia and one developed hypotension. Thus, there was no difference in adverse effects between the groups with p value of 0.389, which was statistically insignificant.

Discussion

Laryngoscopy and tracheal intubation are accompanied by significant increase in arterial blood pressure and heart rate.[14,15,16] Tracheal intubation and extubation causes tachycardia and

hypertension. These hemodynamic changes during anaesthesia may cause increase in myocardial oxygen demand in patients with CAD.[17,18] Significant increase in serum epinephrine and norepinephrine concentrations following laryngoscopy with or without intubation have been described. In the absence of any measures to prevent the hemodynamic response to laryngoscopy, the heart rate and BP can increase much above the acceptable limits. The changes are maximum 1 minute after intubation and last for 5 to 10 minutes. Factors prolonging the pressor response to laryngoscopy and intubation are light plane of anaesthesia, anatomically difficult view, greater force to displace the tongue, prolong time to complete the procedure and numerous manipulations or attempts at laryngoscopy and intubation.[19]

Many attempts have been made to attenuate the pressure response as deeper plane of anaesthesia, topical agents, use of ganglion blocker, phentolamine, MgSO4, beta- blockers, nitroprusside, calcium channel blockers and opioids. [20,21,22] Laparoscopic surgeries allow faster recovery and are associated with marked hemodynamic disturbances. Insufflated CO2 is absorbed from the abdominal cavity into the circulation causing hypercarbia.[23,24] Hypercarbia itself is known to increase arterial pressure and heart rate by activating central nervous system and evoking sympathoadrenal response.[25] Pneumoperitoneum has been shown to increase plasma catecholamine concentration.[26] Elevation may be due to chemoreceptor activation and enhanced sympathetic outflow caused by soluble CO2. [24,27]

Table 2: Comparison of mean blood pressure at different time intervals between 3 groups

	Group C	p-value	Group D	p-value	Group E	p-value
T1	104.21 ± 7.96		103.81 ± 7.79		104.03 ± 5.67	
T2	104.01 ± 7.47	0.485	103.36 ± 7.42	0.123	103.72 ± 5.64	0.233
T3	114.41 ± 5.64	<0.001	102.95 ± 5.6	0.246	103.43 ± 6.16	0.116
T4	113.71 ± 5.87	<0.001	92.49 ± 6.22	<0.001	101.35 ± 7.84	0.001
T5	112.09 ± 5.17	<0.001	90.84 ± 5.38	<0.001	99.77 ± 6.70	<0.001
T6	111.97 ± 5.18	<0.001	90.29 ± 5.37	<0.001	98.58 ± 7.26	<0.001
T7	110.59 ± 5.54	<0.001	91.6 ± 5.36	<0.001	99.21 ± 6.89	<0.001
T8	109.29 ± 5.28	<0.001	90.77 ± 5.22	<0.001	97.03 ± 6.6	<0.001
T9	107.21 ± 7.43	<0.001	96.89 ± 7.38	<0.001	97.73 ± 5.62	<0.001
T10	103.57 ± 5.26	0.594	102.83 ± 4.6	0.325	103.6 ± 5.60	0.577
T11	104.24 ± 5.22	0.982	103.68 ± 4.58	0.891	104.08 ± 5.16	0.938

Miller DR et al [28] studied the effect of single bolus dose of either placebo or esmolol in dose of 100 or 200 mg IV prior to induction for controlling hemodynamic response to tracheal intubation. They found esmolol to be effective in obtunding the response to tracheal intubation and when combined with low dose of narcotics found it to be more effective in controlling BP. In our study esmolol is found to be effective in controlling heart rate. Parvez Gazi et al[29] studied controlled hypertensive patients scheduled for routine surgical procedures divided into 3 groups. First group received 10 ml of 5 % dextrose, second group received diltiazem 0.2 mg/Kg and third group received esmolol 1.5mg/Kg, similar doses were used in our study. They concluded that esmolol is a very effective agent in attenuating the pressor response to laryngoscopy and intubation in controlled hypertensive patients.

Gurudutta KN et al[30] studied the efficiency of intravenous esmolol in the attenuation of hemodynamic response to laryngoscopy and intubation in normotensive individuals. One group of patients received 10 ml of 0.9% normal saline and other received IV Esmolol 100 mg. They concluded that esmolol in a dose of 100 mg given 2 minutes before induction is highly effective in attenuation hemodynamic response to laryngoscopy and intubation. Mikawa et al [31] studied intravenous diltiazem in dose of 0.2 and 0.3 mg/kg versus placebo, they found that diltiazem treated patients showed better control in MAP and heart rate during tracheal intubation, which was consistent with findings in our study.

Nishina K et al [32] studied the effect of diltiazem compared with that of lignocaine and saline as placebo. Inhibitory effect on cardiovascular response was greatest with diltiazem in dose of 0.2 mg/kg. Same dose was used in our study which showed similar findings.

Hans Raj Chauhan et al [33] compared three group of patients. Injection diltiazem 0.2 mg/kg, esmolol 1 mg/kg and normal saline was used as placebo. They found that esmolol was most effective in controlling heart rate, diltiazem was effective in controlling pressor response as seen in our study as well, though the dose of esmolol used in this study was less as compared to our study, the findings were similar. This study showed even lower doses

of esmolol can attenuate pressor response effectively.

Rashmee Chavan et al[34] studied three group of patients. Either esmolol 2 mg/kg IV, diltiazem 0.2 mg/kg IV was given as compared to control group. They found that maximum attenuation of all the parameters was seen in esmolol group followed by diltiazem and then in control group. In our study three groups were studied, though in this study the dose of esmolol used was higher it was found to be effective with minimal side effects. Kumar S et al[35] studied patients to compare the efficacy of IV esmolol, diltiazem and magnesium sulphate for attenuating the haemodynamic response to laryngoscopy and tracheal intubation. They found that esmolol was most effective in attenuating rise in heart rate following laryngoscopy and intubation while the rise in blood pressure was suppressed but not prevented by bolus dose of esmolol (2 mg/kg). In our study also esmolol controlled heart rate better but blood pressure was controlled better by diltiazem.

Dae Heui Nam et al[36] studied patients using saline, diltiazem 0.2 mg/kg and esmolol 1.5 mg/kg. They found that the inhibitory effect on changes of heart rate was greater with esmolol than diltiazem, but the attenuating effect on changes in systolic blood pressure was greater with diltiazem than esmolol. The doses used and findings were similar to our study. In a study by S Umamaheshwara et al [37] patients received esmolol, metoprolol and diltiazem respectively 3 minutes before laryngoscopy and endotracheal intubation. Esmolol found to be more effective in suppressing the haemodynamic responses followed by diltiazem and then by metoprolol. The findings were consistent with our study.

Conclusion:

In our study, we conclude that intravenous esmolol found to be effective in obtunding the rise in heart rate while diltiazem was more effective in controlling the pressor response during laryngoscopy and intubation. During pneumoperitoneum it was observed that, rise in heart rate was better controlled by esmolol, while surge in SBP, DBP, MAP was obtunded more by diltiazem but the effect lasted only till 15 minutes after pneumoperitoneum.

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