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Comparing Effects of Intravenous Esmolol and Diltiazem for Attenuatinghemodynamic Responses to Laryngoscopy and Intubation

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Abstract

Introduction: Laryngoscopy and intubation of trachea are integral part of general anesthesia which can trigger adverse hemodynamic responses. These are unpredictable reflex sympathetic stimulations that may cause tachycardia, hypertension and arrhythmias. These short duration responses get amplified in high risk patients with likelihood of even pulmonary oedema and cerebrovascular accidents. These responses can be blunted by means like drugs and nerve blocks. Our study was designed to compare actions of intravenous (IV) esmolol (1mg/kg) and ditiazem (0.2mg/kg) to attenuate these responses. *Material and Methods:* 80 consenting, ASA I/II adults posted for elective non-cardiac, non- neurologic operations were included in this randomised, double blinded, clinical comparative study. Parameters recorded were ECG, heart rate (HR), systolic BP (SBP), diastolic BP (DBP), mean arterial BP (MAP), ST segment values, SpO2, arrhythmia analysis and incidence of any required rescue medication. Baseline values (mean of three readings, 1 minute apart) of HR, SBP, DBP, MAP, ST segment and SpO_2 were recorded before induction of anesthesia. General anesthesia was given and study drug was injected 1 min. after muscle relaxant and intubation was done 2 min. thereafter. Abovesaid parameter values were recorded at intubation and every minute thereafter, till 10 min. post-intubation. Effects were statistically analysed. *Statistical analysis and results:* Unpaired t-test and generalized estimation equation were used for quantitative variables (e.g. HR, BP) to compare mean levels at different times points between two groups. Paired t-test was used for determining significance within the group at different time points. Chi-square/Fischer exact test (for categorical variable like arrhythmia) and non-parametric Mannwhitney test (in case data did not follow normal distribution) were planned,but were not required. *Results:* Both drugs control the heart rate well. Esmolol controls it better. At 10 minutes after intubation both achieve similar HR values. Both drugs control the SBP, DBP and MAP. Diltiazem controls it better. At 10 min. after intubation, both achieve similar BP values. Both drugs safely attenuate hemodynamic response to laryngoscopy and intubation, as there were no arrhythmias, ST changes of significance or requirements of rescue medications in any patient.

Keywords: Laryngoscopy; Tracheal Intubation; Hemodynamic Response.

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Introduction

Laryngoscopy and tracheal intubation are integral part of anesthesia since their first description, in 1921, by Rowbotham& Mc Gill [1]. Reid & Brace [2] recognised that these procedures trigger adverse hemodynamic responses These sympathetic reflexes, due to epipharyngeal & laryngeal stimulation, cause tachycardia, hypertension & arrhythmias [3,4].

These short lived, variable & unpredictable responses

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get amplified in hypertensives [5] and highrisk patients with cardiovascular & cerebrovascular disease, anomalies of cerebral vessels and raised ICP [6]. Such patients may even get pulmonary oedema [7], myocardial insufficiency & CVA [8]. Blunting of them can be achieved by means like drugs and nerve blocks.

We designed our study to compare blunting of hemodynamic response to laryngoscopy & intubation by Esmolol and Diltiazem.

Material and Methods

After hospital ethics committee's approval,80 consenting, ASA I/II adult patients (18-60 years old) of either sex, posted for elective non-cardiac and non-neurologic surgeries were enrolled in our study. Patients were randomly divided into 2 groups of 40 each (Group1 & Group 2) according to a computerised random table.

Group 1 received Inj. Esmolol - 1mg/kg and Group 2 received Inj. Diltiazem – 0.2 mg/kg, both 2 minutes before laryngoscopy.

An independent investigator prepared the study drug, diluted it to 10 ml., not disclosing the name to worker inducing anesthesia till the end of the study on that patient.

All patients were fasted overnight. All patients received tablet ranitidine–150 mg and tablet alprazolam 0.25 mg the night before surgery. In Operation theatre, IV line and monitors were attached.

Three readings each of HR, SBP, DBP, MAP, ST segment value, 1 minute apart, were taken. Mean of three values of each parameter were recorded as baseline value.

Induction of anesthesiawas done in sequence for all patients, i.e., fentanyl-2 mic/kg, 3 min. of proxygenation, thiopentone-4-6 mg/kg till loss of eyelash reflex, check ventilation, vecuronium - 0.1 mg/kg, mask ventilation with 50:50, O_2+N_2O and 1% isoflurane,

Study drug was injected 1 min. after vecuronium. Group 1 received Inj. Esmolol - 1mg/kg and Group 2 received Inj. Diltiazem – 0.2 mg/kg, both 2 minutes before laryngoscopy. Laryngoscopy was done 2 min. after study drug by ananesthesiologist with experience of more than 100 laryngoscopies.

Anesthesia was maintained with 50:50 - O_2+ N_2O and 1 % isoflurane for next 10 minutes. HR, SBP, DBP, MAP & ST segment values were recorded at 0, 1, 2, 3, 4, 6, 8, 10 minutes starting with time of laryngoscopy. No painting, draping or surgery was done during the period of observation

Statistical Analysis

Assuming the mean difference in systolic blood pressure as 10±6.4(9) in the esmolol group and diltiazem group 8±0.9, taking as 20% mean difference between both the drugs, a = 0.05 and power = 80% the minimum number of subjects under each group would be 35, however, 40 patients were taken in each group.

For quantitative variables such as systolic blood pressure, diastolic blood pressure and heart rate the mean level was compared at different points of time between two groups by unpaired student t-test, and generalised estimation equation. In case data do not follow a normal distribution the parametric Mannwhitney test would be applied, however it was not necessary to apply in our study as the data had a normal distribution. For determining the statistical significance within each group over a different point of time, the paired t-test were applied.

For categorical variable (eg. Arrhythmia) the Chi-square / Fischer exact test was planned to be applied, however, it was not needed in our study as there was no incidence of arrythmia. Statistically significant level was considered as p=0.05.

Observations and Results

The demography of two groups was similar statistically (Table 1).

Table 1: Demographic Profile

		Esmelol	Diltiazem	p value
Age	Range	19-60	18-55	
	Mean	32.25	34.95	p=0.382
	Standard Deviation	11.83	11.58	(p>0.05)
Weight	Range (kg)	30-80	30.75	
	Mean	54.87	55.55	p=0.786
	Standard Deviation	12.45	9.44	(p>0.05)
Gender	Male	18	19	
	Female	22	21	

Fig. 1:

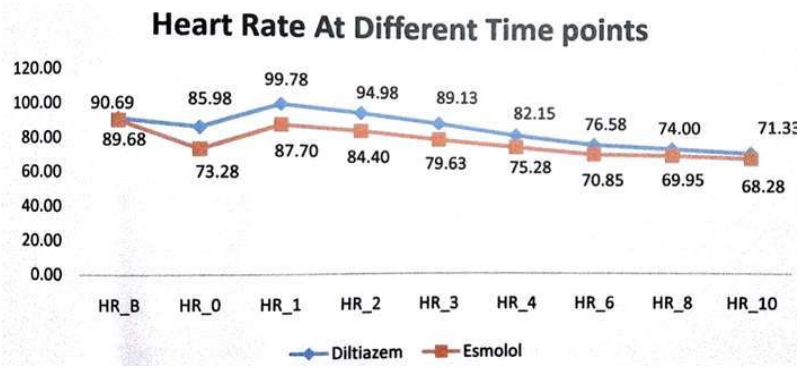


Fig. 2:

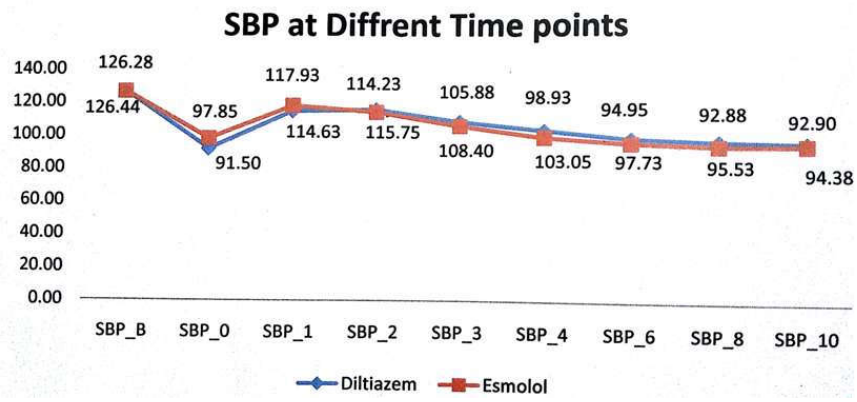


Table 2: Comparison of esmolol and diltiazem on systolic blood pressure (SBP) at different points

Heart Rate	Diltiazem	Esmolol	P value
HR Baseline	90.7± 16.1	89.68± 13.55	0.763
HR0	85.98± 12.54	73.28± 8.74	0
HR1	99.78± 14.25	87.7± 11.41	0
HR2	94.98± 14.42	84.4± 11.75	0.001
HR3	89.13±14.92	79.63± 10.81	0.002
HR4	82.15± 13.24	75.27± 10.63	0.012
HR6	76.58± 12.43	70.85± 10.53	0.029
HR8	74± 13.32	69.95± 10.48	0.134
HR10	71.33± 12.98	68.27± 10.39	0.249

Table 3: Comparison of esmolol and diltiazem on diastolic blood pressure at different time points

SBP	Diltiazem	Esmolol	P value
SBP Baseline	126.44±11.69	126.28±13.76	0.955
SBP0	91.5±4.62	97.85±13.02	0.004
SBP1	114.63±14.69	117.9±18.35	0.377
SBP2	115.75±14.35	114.3±17.32	0.669
SBP3	108.4±11.18	105.8±15.64	0.408
SBP4	103.05±10.06	98.9±10.11	0.071
SBP6	97.73±8.97	94.95±6.97	0.126
SBP8	95.53±8.88	92.9±5.22	0.108
SBP10	94.38±6.46	92.9±6.03	0.294

Esmolol caused significant fall of HR from baseline at all times, except 1 minute after laryngoscopy (not significant), ultimately causing fall of 24% at 10 minutes post-laryngoscopy Diltiazem caused significant fall of HR at all times, except a significant rise, 1 minute after laryngoscopy, till a 21% fall at 10 minutes post-laryngoscopy. Unpaired t-testing revealed the two drugs reduce HR similarly from 2 minutes post-laryngoscopy (Table 2 and Graph 1).

Both drugs caused significant SBP fall at all time intervals. Diltiazem caused greater fall than esmolol. SBP fell similarly in both groups at all times (Table 3 and Graph 2).

Both drugs caused significant fall of DBP from baseline at all times, except at 1minute post-laryngoscopy (fall not significant). Both drugs reduced DBP similarly at all times (Table 4 and Graph 3).

Both drugs cause significant fall of MAP at all times after injection, except 1 minute post-laryngoscopy (fall not significant). Both drugs affect MAP similarly at all observed times (Table 5 Graph 4).

Table 4: Comparison of esmolol and diltiazem on mean arterial pressure at different time points

DBP	Diltiazem	Esmolol	P value
DBP Baseline	78.62±9.50	80.71±9.72	0.333
DBP0	54.27±7.13	60.20±12.27	0.010
DBP1	76.05±13.65	78.15±16.01	0.529
DBP2	71.95±13.09	73.05±14.18	0.719
DBP3	66.73±9.36	66.55±13.36	0.946
DBP4	62.4±8.82	61.98±8.08	0.822
DBP6	58.75±8.27	57.9±5.59	0.591
DBP8	57.23±8.48	56.13±4.43	0.469
DBP10	56.25±8.33	55.85±4.91	0.794

Table 5: Comparison of the effect of both the Drugs on mean arterial pressure at different time points

MAP	DILTIAZEM	ESMOLOL	P VALUE++
MAP Baseline	94.55±9.63	95.90±10.26	0.55
MAP0	66.68±5.69	72.75±11.84	0.00
MAP1	88.91±13.15	91.41±16.09	0.45
MAP2	86.55±12.93	86.78±14.85	0.94
MAP3	80.62±9.40	79.68±13.77	0.72
MAP4	75.75±8.74	74.29±8.27	0.39
MAP6	71.74±8.14	70.25±5.39	0.34
MAP8	69.99±8029	68.38±3.94	0.27
MAP10	68.96±7.28	68.2±4.52	0.58

Fig. 3:

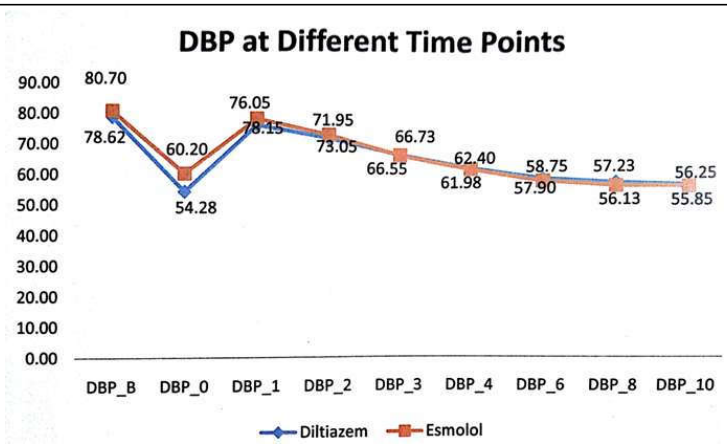
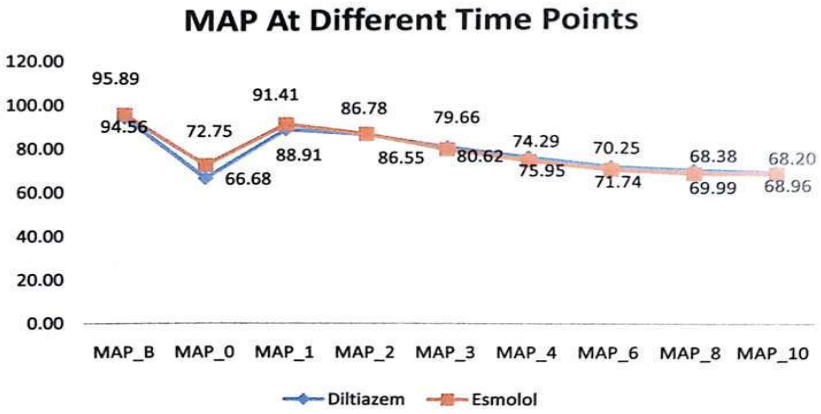


Fig. 4:



Discussion

Laryngoscopy and tracheal intubation are an integral step of anaesthetic practice and associated with stress response of increased blood pressure, heart rate and cardiac dysrhythmias [1-4].

This stress response may be transitory but can have adverse outcome in high risk patients like those with cardiovascular diseases, increased intracranial pressure or anomalies of cerebral vessels [5-8].

An increase in mean arterial pressure of 25mm of Hg and 20-40 torr when compared with awake control levels and 35-60 torr when compared with pre-intubation values [3] have been reported after the placement of endotracheal tube.

The purpose of our study was to observe the effects of esmolol and diltiazem, which are known to alter the hemodynamic response to laryngoscopy and tracheal intubation and compare their effects.

Esmolol on heart rate:

In our study, esmolol caused a statistically significant decrease in heart rate till the time of laryngoscopy, heart rate increased to baseline values 1 minute after laryngoscopy, after which it continued to fall for 10 minutes.

In the study done by Kumar S [9] in the year 2003 to compare the efficacy of esmolol, diltiazem,and magnesium sulphate in attenuation of hemodynamic response to laryngoscopy and intubation, there was a similar decrease in heart rate till laryngoscopy, insignificant rise in heart rate immediately after intubation with a gradual decrease after that. These findings are similar to our findings.

In the study done in 1990 by Oxorn [10] who compared two doses of esmolol (100 mg and 200 mg) with placebo, there was fall in heart rate following laryngoscopy and tracheal intubation with both doses. In our study there was a statistically significant fall before and till 10 minutes after laryngoscopy and intubation, compared with baseline values. The findings of the above study are in accordance with our study.

In a study done by Helfman SM et al. [11] in 1991 to compare the efficacy of lignocaine, fentanyl and esmolol it was concluded that esmolol reliably attenuated the rise in heart rate. This is also in accordance with our study where esmolol has prevented any rise of heart rate above the baseline value.

In another study conducted by Yuan et al. [12] in the year 1994 to compare the effects of two different bolus doses of esmolol it was found that there was significant fall of heart rate following administration of both 100mg and 200 mg of esmolol. In our study there was also significant decrease in heart rate following esmolol administration.

In the year 1996 Feng and Chan et al. [13] studying the effects of lidocaine, fentanyl and esmolol in attenuation of hemodynamic response to laryngoscopy and tracheal intubation found the incidence of tachycardia in 15% patients administered with esmolol. In our study there was no incidence of tachycardia in any patient administered with esmolol.

Another study conducted by Sharma et al. [14] in 1996 to compare the efficacy of two bolus doses of esmolol it was found that 100mg IVbolus of esmolol maintained heart rate comparable to baseline values whereas 200mg esmolol IV bolus resulted in heart rate lower than baseline values. In our study, the heart rate remained statistically significantly lower than the baseline values at all the time intervals except the 1st minute following laryngoscopy and tracheal intubation.

It is notable that we used (as per the hospital protocol for ASA 1 and 2 patients) isoflurane and fentanyl along with the study drugs.

Effect of Esmolol on Blood Pressure

In our study,Esmolol decreased SBP,DBP and MAP at all study times with a slight rise immediately after intubation (which however was still below baseline).

In 2003 Kumar S [9] compared the efficacy of esmolol, diltiazem and magnesium sulphate in attenuation of hemodynamic response to laryngoscopy and tracheal intubation. They reported less rise of blood pressure in esmolol group after laryngoscopy than control group, however post-laryngoscopy blood pressures were significantly higher than baseline values. These findings are different from ours.

In 1990, Oxorn D, Hill J. et al. [10] studied the effects of IV bolus esmolol 100mg, 200mg and placebo. They reported that SBP was below baseline with 200mg group only. As per the protocol of anaesthesia followed by us, 1mg/kg esmolol was sufficient to attenuate hypertensive response.

Helfman SM et al. [11] in 1991, conducted a study to compare the efficacy of 200mg lignocaine, 200mcg fentanyl and 150mg of esmolol in attenuation of hemodynamic response to tracheal intubation. They concluded that esmolol alone reliably controlled the hypertensive response. This is similar to our study.

In the year 1994 Yuan et al. [12], studied the effect of single bolus dose of esmolol in two doses of 100mg and 200mg resulted in significant decrease in SBP till 8 minutes after laryngoscopy. Use of only 1mg/kg esmolol in our study along with our protocol of anaesthesia ensured similar results.

Feng &chan et al. [13], studying lidocaine, fentanyl, esmolol (2mg/kg) found only esmolol reliably controlled the pressor response. We found a dose of 1mg/kg to be effective controller of pressor response.

In 1996, Sharma et al. [14] compared the efficacy of two bolus doses of esmolol to blunt this pressor response in treated hypertensives. Esmolol 100 mg maintained ABP & HR compared to basal values ($p>0.05$), whereas esmolol 200 mg showed lower than basal values throughout the study. Our study shows esmolol 1mg/kg effectively attenuates response.

Diltiazem on HR

Kumar S [9], reported rise of HR after diltiazem injection & further rise after laryngoscopy for 5 minutes. They used glycopyrrolate, diazepam & halothane. Use of glycopyrrolate, probably contributed to such a high rise of HR. With our protocol, for first three minutes after intubation, HR was near baseline or more than that.Thereafter, significant reduction of HR was noted.

In 1996 Mikawa et al. [15], compared the effect of nicardipine, verapamil and diltiazem in controlling the cardiovascular response to tracheal intubation. They found that the heart rate increased before and after laryngoscopy. The rise of HR was statistically significant till 5 minutes post intubation. In our study there was a significant fall in heart rate, following drug administration, just before laryngoscopy and a significant rise in heart rate 1 min after intubation. The heart rate decreased below the baseline values after 3 minutes.

Nishina et al. [16] in 1995 conducted a study on effect of diltiazem in attenuation of cardiovascular response to tracheal extubation and emergence from anaesthesia. They found that IV diltiazem in both doses (0.1mg/kg and 0.2mg/kg) failed to attenuate the increase in heart rate following tracheal extubation. In our study (conducted for intubation) the heart rate also increased 1 min. after tracheal intubationand then gradually decreased.

In 1990 Mikawa et al. [17] investigated the effect of diltiazem on cardiovascular response to tracheal intubation and found that IV diltiazem given 1 minute before laryngoscopy failed to protect against increase in heart rate after laryngoscopy. In our study there occurred significant rise in heart rate 1 minute following laryngoscopy and tracheal intubation but there after it gradually decreased to less than baseline by the 10th minute.

Diltiazem on Blood Pressure

In our study, diltiazem caused statistically significant fall in SBP, DBP and MAP just before laryngoscopy which increased1 minute after intubation& then continued to decrease till 10 minutes after intubation. At all times the parameters were less than the baseline values.

In the study of Kumar S [9], it was found that there was statistically significant fall of SBP and DBP following its administration. Both SBP and DBP increased above the baseline value 1 minute after intubation and then continued to decrease till 5 minutes. As per the protocol of anaesthesia followed by us using diltiazem 0.2mg/kg, though SBP and DBP followed similar trend but at no time , the values were more than the baseline reading.

In the study done by Mikawa et al. [15], to compare the efficacy of diltiazem, verapamil and nicardipine to control pressor response tracheal intubation, they found that diltiazem 0.2mg/kg given as per their protocol (diazepam, fentanyl, thiopentone, vecuronium, preceded by two doses of atropine premedication) caused significant increase in SBP and DBP after tracheal intubation followed by a decrease in both the parameters till 5 minutes. As per the protocol of anaesthesia followed by us using diltiazem 0.2mg/kg , though SBP and DBP followed similar trend but at no time , the values wkjere more than the baseline reading.

Kahorunishina et al. [16], conducted a study on effect of diltiazem in attenuation of cardiovascular response to tracheal extubation and emergence from anaesthesia and found that IV diltiazem in dose of 0.2mg/kg attenuated the pressor response to tracheal extubation. This is like our study of diltiazem for intubation.

Mikawa et al. [17], found that IV diltiazem given 1 minute before laryngoscopy attenuated the cardiovascular response. This is like our study of diltiazem for tracheal intubation.

Limitations of Our Study

- Depth of anaesthesia was monitored only clinically.
- Degree of neuromuscular relaxation was monitored clinically and observing CO_2 graph.

- Fentanyl and isoflurane are known to modulate response to laryngoscopy and intubation.

Conclusions and Recommendations

Based on the present double blinded clinical comparative study, the following conclusions canbe made.

- Both esmolol and diltiazem cause statistically significant fall of systolic blood pressure, diltiazem more than esmolol until laryngoscopy.
- The systolic blood pressure remains low similarly with both the drugs after laryngoscopy and intubation.
- Both esmolol and diltiazem cause statistically significant fall of diastolic blood pressure, diltiazem more than esmolol until laryngoscopy.
- The diastolic blood pressure remains low similarly with both the drugs after laryngoscopy and intubation.
- Both esmolol and diltiazem cause statistically significant fall of mean arterial pressure, diltiazem more than esmolol until laryngoscopy.
- The mean arterial pressure remains low similarly with both the drugs after laryngoscopy and intubation.
- There were no episodes of arrhythmia or significant ST changes in any patient.

Thus, esmolol causes better hemodynamic attenuation of response to laryngoscopy and tracheal intubation, than diltiazem.

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