ORIGINAL ARTICLE

Comparison of effect of esmolol vs. esmolol and fentanyl on hemodynamic response to laryngoscopy and tracheal intubation in controlled hypertensive patients: a randomized controlled double blind study

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ABSTRACT

Background: Direct laryngoscopy and endotracheal intubation result in tachycardia and hypertension. This response is exaggerated in hypertensive patients who are at risk of cardiovascular or cerebrovascular events. The objective of present study was to evaluate the pressor response in controlled hypertensive patients, and compare the effects of esmolol with a combination of esmolol and fentanyl.

Methodology: The study was conducted in 90 controlled hypertensive patients posted for surgery under general anesthesia. The patients were randomized into three equal groups to receive normal saline (Group C = 30 patients), esmolol 1.5 mg/kg (Group E = 30 patients) and esmolol 1.5 mg/kg with fentanyl 2 μg/kg (Group EF = 30 patients). Following study drugs anesthesia induced with thiopentone 5 mg/kg, intubated with suxamethonium 1.5 mg/kg and maintained with 66% nitrous oxide, oxygen and isoflurane 0.6-1.2 vol%. Heart rate and arterial pressure were recorded at baseline, immediately after intubation, 1, 3, 5 and 7 minutes post-intubation.

Results: In all 3 groups, the rise in heart rate and blood pressure was the highest at one minute post-intubation and immediately after intubation respectively. Heart rate was significantly high in Group C compared to other groups at all time intervals and there was no difference between Groups E and EF. Blood pressure was significantly different at all time intervals between Groups C and E, between C and EF and between E and EF. 43% of patients in Group EF had significant hypotension during study period.

Conclusion: Esmolol 1.5 mg/kg is effective in attenuating haemodynamic response to laryngoscopy and intubation in controlled hypertensive patients. Esmolol 1.5 mg/kg with fentanyl 2 μg/kg should be used cautiously as it causes hypotension following intubation.

Keywords: Hemodynamic response; Tracheal intubation; Hypertensive patients; Esmolol; Fentanyl

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INTRODUCTION

Laryngoscopy and intubation usually causes rise in heart rate and blood pressure. Various pharmacological agents e.g. β-blockers, calcium channel blockers, nitroglycerine, opioids, α_2 adrenergic agonists, inhalational anesthetics, pregabalin, lornoxicam, lidocaine etc., have been used to suppress this response.[1-8] In hypertensive patients, the pressor response to intubation is more marked than in normotensives.[9]

The prevalence of hypertension in Indian population is 25%[10] and there is an increase in the proportion of patients with co-existing hypertension presenting for surgery. These patients have high incidence of cardiac arrhythmias, myocardial ischemia, acute left ventricular failure and cerebrovascular accidents following intubation.[9,11,12] Hence, suppression of intubation response is always desirable.

Fentanyl is a synthetic phenethylpiperidine derivative opioid agonist. It modulates the nociceptive input and has been used at low doses to attenuate the pressor response.[13,14] Similarly, cardio-selective, β-blocker esmolol which has a short half-life has been used as bolus[15,16], infusion[17,18] and at low doses[19] to suppress the intubation response with mixed results. Multimodal therapy rather than a single intervention has been in practice to attenuate hemodynamic response to laryngoscopy and intubation. Esmolol has been combined with lidocaine[4] or fentanyl[20] for this purpose. All of these studies were conducted in normotensive patients.

In 2003, regulatory bodies such as World Health Organization[21] and 'Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure'[22] have revised guidelines to define hypertension as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. There are limited reports in the literature on attenuation of pressor response in hypertensives particularly using esmolol and combination of esmolol with fentanyl[23,24] and these were done before 2003.

The present study has incorporated latest guidelines of hypertension with the objective of studying hemodynamic response in controlled hypertensive patients, the effectiveness and safety of esmolol 1.5 mg/kg and combination of esmolol1.5 mg/kg with fentanyl 2 μg/kg on intubation response in controlled hypertensive patients.

METHODOLOGY

The study protocol was approved by an Institutional Ethics Committee. It was conducted for a period of 8 months and written consent was obtained from the participants before the study. It was a prospective, randomized, double blind study which included 90 hypertensive patients of American Society of Anaesthesiologists physical status (ASA PS) II of either sex, aged between 35-70 years, weighing ≤ 70 kg and with systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg posted for surgery under general anesthesia. The type of antihypertensive medication and coexistence of bronchial asthma, chronic obstructive pulmonary disease, diabetes mellitus and ischaemic heart disease were noted. Exclusion criteria included patients with ASA PS III and above, anticipated difficult airway, pregnancy, cardiac and neurosurgical procedures, intubation requiring second attempt and intubation prolonged for more than 25 sec. All patients were evaluated by a physician and an anesthesiologist on the previous day of surgery and were premedicated with oral diazepam 5 or 10 mg in the night and morning of surgery. Intramuscular butorphanol 1 mg was given to all one hour prior to surgery. Antihypertensive medications, with the exception of diuretics, were continued until morning of surgery.

Patients were randomized by computer generated random number table into following 3 groups: Group C; 30 patients to receive normal saline (Control), Group E; 30 patients to receive esmolol 1.5 mg/kg and Group EF; 30 patients scheduled to receive esmolol 1.5 mg/kg + fentanyl 2 μg/kg. Sealed envelopes containing group number written on a slip were taken out by an unconnected anesthesiologist who also loaded the drugs in 2 syringes. 5 ml syringe contained fentanyl 2 μg/kg or saline and 10 ml syringe contained 1.5 mg/kg esmolol or saline. A 5 ml and a 10 ml filled syringe were used in every patient. Investigator-1, who was blinded to the study drugs, administered the drugs and also recorded the parameters. Investigator-2, who was also blinded, performed laryngoscopy and intubation in all of the patients. In this way, the evoked stimulus was presumed to be similar for all of the patients.

On arrival in the operation room, patient was connected to basic monitors, e.g. pulse oximetry, non-invasive oscillometric blood pressure, electrocardiogram lead II, V_5. Patients were prehydrated with ringers lactate 5 ml/kg for a resting period of 10 minutes. Heart rate (HR), SBP, DBP and mean arterial pressure (MAP), noted at the end of 10 minutes were considered as baseline values. The patients with baseline BP exceeding 168/108 mmHg (20% above 140/90 mmHg) were excluded from the study. All patients were preoxygenated for 3 minutes. Investigator-1 injected contents of 5 ml syringe over 10 seconds followed by contents of 10 ml syringe over 30 seconds, standard general anesthesia with thiopentone 5 mg/kg followed by suxamethonium 1.5 mg/kg. One minute later, Investigator-2 performed laryngoscopy and intubation, so that it coincided with 2 minutes post-injection of esmolol. Anesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane 0.8-1.2 vol% (Datex Ohmeda Cardiocap 5 monitor). Post-intubation, all the patients received 0.07 mg/kg vecuronium as muscle relaxant.

All study parameters were recorded immediately after intubation (IAI) i.e 10 seconds following intubation, and at 1, 3, 5 and 7 minutes post-intubation. Side effects such as pain on injection, bronchospasm, muscle rigidity and ECG changes in rhythm or ST segment/T wave were noted. In patients with bradycardia (HR □ 60/minute) would be treated with inj. atropine and in case of hypotension (SBP □ 20% baseline) IV fluid bolus and inj. ephedrine 5 mg increment would be given. In case of hypertension (SBP >30% baseline) or tachycardia (HR > 110/min), inspired concentration of isoflurane increased by 0.2-0.4 vol%. The highest reading from baseline value was taken as intubation response.

Statistical Analysis: Statistical tests were performed using SPSS version 16.0. Based on a previous study[25], a sample size of 30 per group with type I error of 0.05 and type II error of 0.20 for 25% difference in MAP between groups was calculated, hence a total of 90 patients were included. Continuous variables were expressed as mean

± standard deviation. Hemodynamic responses within a group were measured using repeated measures ANOVA with Bonferroni`s correction. For categorical variables, Chi-squared or Fisher`s exact test was used. P value <0.05 was considered as statistically significant.

RESULTS

All three groups were comparable with regard to age, weight, sex distribution, type of antihypertensive medications, duration of laryngoscopy, and pre-operative HR and arterial pressure (Tables 1 & 2).

Table 1: Demographic profile of study population

Variables	Groups			P value
	Control (n=30)	Esmolol (n=30)	Esmolol + Fentanyl (n=30)	
Age (years)#	57.9±11.2	61.6±9.09	59.4±8.9	0.352
Weight (kg)#	56.7±9.6	53.8±9.3	54.6±7.5	0.416
Gender (M/F)	19/11	20/10	20/10	0.954
Duration of laryngoscopy (sec)#	12.6±1.9	12.2±1.9	12.3±1.8	0.598
HR*#	83.0±16.6	79.3±14.6	80.7±15.5	0.658
SBP*#	146.4±13.1	149.3±14.3	144.7±12.8	0.404
DBP*#	89.5±7.7	86.8±10.1	88.5±8.1	0.501
MAP*#	108.4±8.2	107.6±10.1	107.2±8.7	0.875

Values in Mean±SD, * Preoperative ward readings.

Table 2: Antihypertensive medication details

Details of antihypertensive medications	Number of patients		
	Control (n = 30)	Esmolol (n = 30)	Esmolol + Fentanyl (n = 30)
1. ACE inhibitor*	4	4	3
2. β-blocker	1	3	3
3. Calcium channel blocker	19	15	13
4. Diuretic	1	-	-
5. ACE inhibitor*			
+ β-blocker	-	-	1
+ Calcium channel blocker	1	2	2
+ Diuretic	-	1	2
+ Angiotensin receptor antagonist	1	-	-
+ Calcium channel blocker + diuretic	-	1	-
6. β-blocker			
+ Calcium channel blocker	1	3	5
+ Diuretic	1	-	-
7. Calcium channel blocker			
+ Diuretic	-	1	1
+ β-blocker + clonidine	1	-	-

* ACE inhibitor – Angiotensin converting enzyme inhibitor

Following laryngoscopy and tracheal intubation, HR was increased at 1 minute post-intubation from the baseline in all three groups, which is statistically significant (P<0.01). The rise in HR was 32% (CI: -31.14 to -20.99) in Group C (P<0.01), 14% (CI: -16.88 to -6.38) in Group E (P<0.01), and 10% (CI: -13.50 to -4.30) in Group EF (P<0.01). HR was significantly lower in Groups E and EF compared to Group C at all-time intervals (P<0.01). However, there was no difference between Groups E and EF (P=1.00). HR did not reach baseline value in any of the groups at 7 minute post-intubation (Figure 1).

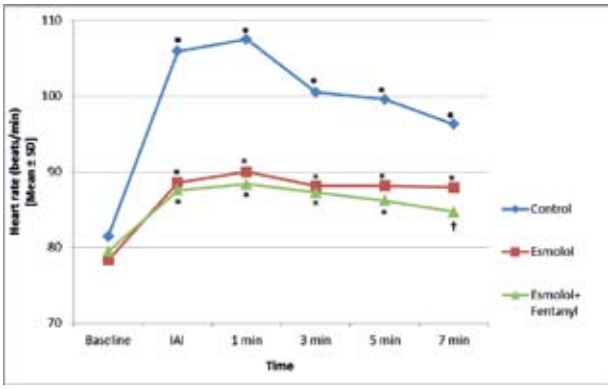

Figure 1: Comparison of heart rate (mean±SD) between control, esmolol and combination of esmolol+fentanyl.

IAI – Immediately after intubation; * indicates significant difference from baseline; † indicates non-significant difference from baseline.

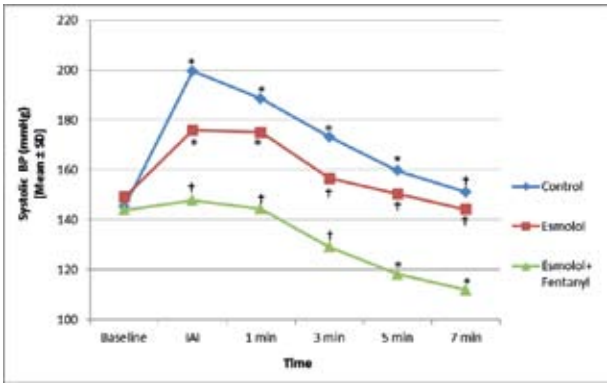

Figure 2: Comparison of systolic blood pressure (mean±SD) between control, esmolol and combination of esmolol+fentanyl.

IAI – Immediately after intubation; * indicates significant difference from baseline; † indicates non-significant difference from baseline.

Arterial pressure increased in all three groups immediately after intubation (IAI) from the baseline. The rise in SBP was 37% (CI: -60.84 to -47.63) in Group C (P<0.01), 18% (CI: -33.39 to -20.21) in Group E (P<0.01) and 3% (CI: -10.88 to -2.74) in Group EF (P<0.01). A significant rise in SBP was observed up to 5 minute post-intubation in Group C and up to 1 minute post-intubation in Group E. However, in Group EF there was no significant rise in SBP, instead there was a significant hypotension from 3

to 7 minute post-intubation (P<0.01). Between Groups C and E, a significant difference in SBP was observed from IAI up to 3 minute post-intubation (P<0.01). In between Groups C and EF and between Groups E and EF, the differences were significant at all time intervals (P<0.01) (Figure 2).

The rise in DBP was 51% (CI: -52.54 to -39.19) in Group C (P<0.01), 28% (CI: -29.58 to -18.95) in Group E (P<0.01), and 13% (CI: -16.09 to -6.64) in Group EF (P<0.01). A significant rise in DBP was observed from IAI to 7 minute post-intubation in Group C and from IAI up to 3 minute post-intubation in Group E. Whereas, in Group EF, there was a significant rise at IAI and 1minute post-intubation followed by hypotension until 7 minute post-intubation (P<0.01). There was a significant difference in DBP between Groups C and E from IAI up to 5 minute post-intubation. In between Groups C and EF and between Groups E and EF, the differences were significant at all time intervals (P<0.01) (Figure 3).

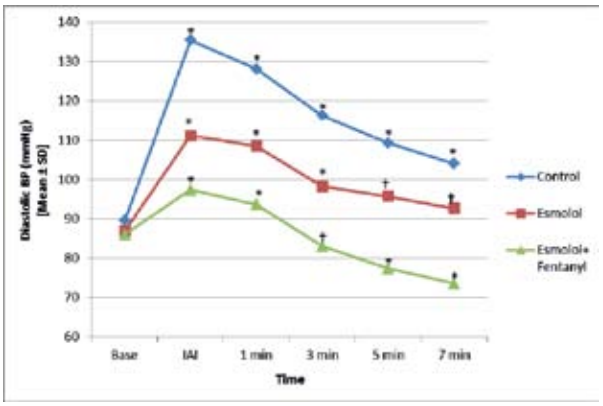

Figure 3: Comparison of diastolic blood pressure (mean±SD) between control, esmolol and combination of esmolol+fentanyl.

IAI – Immediately after intubation; * indicates significant difference from baseline; † indicates non-significant difference from baseline.

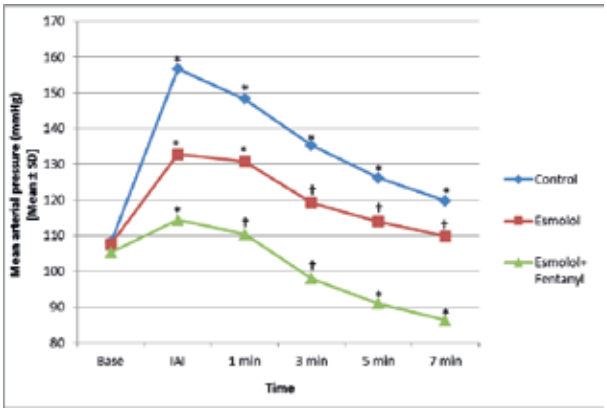

Figure 4: Comparison of mean arterial pressure (mean±SD) between control, esmolol and combination of esmolol+fentanyl

IAI – Immediately after intubation; * indicates significant difference from baseline; † indicates non-significant difference from baseline.

The rise in MAP from baseline was 45% (CI: -55.05 to -42.35) in Group C (P<0.01), 23% (CI: -30.24 to -20.22) in Group E (P<0.01) and 9% (CI: -14.41 to -3.79) in Group EF (P<0.05). Change in MAP mirrored changes in DBP and is as shown in (Figure 4).

Adverse events observed during the study are shown in Table 3. Significant number of patients in Group C had tachycardia and hypertension (P<0.01). Tachycardia and hypertension responded to deepening plane of anesthesia with inhalational anaesthetic. Heart rate decreased below baseline value in few patients, which was statistically not significant (p=0.328) and it did not fall below 60/min. Hypotension responded to intravenous fluid bolus and injection ephedrine 5 mg bolus. 9 (10%) out of 90 patients had rhythm changes which included ventricular bigeminy, atrial ectopics and ventricular premature beats following intubation, which was benign and self limiting. No significant difference in incidence of arrhythmias was observed among the groups. No incidence of ST segment or T wave changes was observed. None of the cases had any bronchospasm or chest wall rigidity.

Table 3: Adverse effects observed

Variables	Groups			P value
	Control (n = 30)	Esmolol (n = 30)	Esmolol + Fentanyl (n = 30)	
Bradycardia	1	4	5	0.328
Tachycardia	21*	3	1	0.000
Hypotension	2	4	13†	0.001
Hypertension	20*	1	0	0.000
Pain on injection	0	4‡	0	0.032
Arrhythmia	3	4	2	0.905
Smoking	7	6	7	0.938

* Significant difference in Control group compared to other two groups.

† Significant difference in Esmolol+Fentanyl group compared to other two groups.

‡ Significant difference in Esmolol group compared to other two groups.

DISCUSSION

There has been a constant search among anesthesiologists to find an ideal agent to attenuate the intubation response. Chung F. and McCammon R. L. observed that laryngoscopy was responsible for rise in arterial pressure and tracheal intubation caused rise in heart rate. [26,27] This is consistent with our study where maximum rise in BP occurred immediately after intubation and HR was

highest at one minute post-intubation. Forbes AM[28] stated that HR and BP returned to pre-laryngoscopy level in normotensives within 5 to 10 minutes due to adaptation and gradual fatigue of receptors, cessation of stimulus and deepening of anesthesia. However, Chandola HC observed that in hypertensive patients, in whom pressor response was exaggerated it took as long as 20 minutes to reach the baseline value.[29] This is consistent with findings of the present study where HR and BP in control group did not reach baseline value even after 7 minutes.

Since the introduction of esmolol in 1982, it has found clinical application to control perioperative tachycardia and hypertension, to suppress intubation and extubation response, supraventricular tachycardia etc., and has been used as bolus and infusion to attenuate intubation response in doses varying from 0.4mg/kg to 2 mg/kg.[4,15-20,30,31] Studies have consistently found esmolol to blunt the rise in HR to intubation. However, its role in controlling BP has shown mixed results. Most of the studies[4,15-20,23,24,30,31] have shown esmolol to blunt BP response while Hussain[32] and Korginen,[33] who used 2 mg/kg esmolol two minutes prior to intubation, did not find significant attenuation of blood pressure. A meta-analysis done to study effect of esmolol on hemodynamic response stated that esmolol produces a dose dependant suppression of response to laryngoscopy and intubation.[34] Low dose fentanyl is routinely used before induction during general anesthesia. Ko SH[35] found that 2 μg/kg of fentanyl administered 5 minutes before intubation, effectively decreased HR and BP. Fentanyl 3 μg/kg administered 2 minutes before failed to protect against BP response.[36] Yushi U[37] stated that 2 μg/kg fentanyl attenuated hemodynamic response during fibreoptic intubation but failed to protect against direct laryngoscopy and intubation.

In the present study, we found that hypertensive patients exhibited exaggerated pressor response. Esmolol, alone or with fentanyl, significantly attenuated intubation response. Addition of fentanyl to esmolol had no benefit on attenuating HR response but it attenuated BP response better than esmolol alone, albeit at the risk of causing post-intubation hypotension. Sharma[23] stated that 100 mg esmolol was effective on HR response while 200 mg attenuated BP response in hypertensive patients. Relatively few investigations have combined esmolol with fentanyl. Sam Chung[24] studied effects of esmolol 2 mg/kg bolus alone or in combination with fentanyl 2 or 5 μg/kg and found that the combination blunted hemodynamic response. Donald Miller[38] did a multicentre trial using esmolol bolus 100-200 mg bolus or in combination with low (2-3 μg/kg fentanyl) or moderate (4-7 μg/kg fentanyl) and found that esmolol with low dose fentanyl was effective in controlling HR and BP. Cheng MH[24] studied 60 hypertensive patients divided in four groups and concluded that 2 mg/kg esmolol or 2 μg/kg fentanyl can partly reduce hemodynamic response but esmolol 2 mg/kg with fentanyl 2 μg/kg completely attenuate hemodynamic and catecholamine response in hypertensive patients. The present study is consistent with results of Donald Miller.[38]

Although tachycardia is the usual response to intubation, 10 patients in the present study had bradycardia. Similar observation was made by Prys-Roberts C,[9] where 3% hypertensive patients developed bradycardia to laryngoscopy and tracheal intubation. Elderly age, preoperative β-blockade, negative chronotropic effect of esmolol combined with central vagomimetic action of fentanyl and addition of Vecuronium could be the reason for decrease in HR following laryngoscopy and intubation.

In the present study, 2 patients in Group C, 4 in Group E and 13 in Group EF have experienced hypotension; all of them have responded to IV fluid bolus and ephedrine. Splinter WM[39] noticed 35 % incidence of hypotension following intubation in geriatric patients after a bolus of 3 μg/kg Fentanyl. Donald Miller[38] observed similar magnitude of hypotension in EF Group. Elderly age, preoperative antihypertensive medications combined with intra operative β-blockade, opioid and vecuronium combination could be the plausible reasons for post-intubation hypotension in E and EF Groups. Hypertensive patients are in a state of chronic volume contraction and are prone for intra operative BP fluctuations. Two patients in Group C had post-intubation hypotension although they had received 5 ml/kg crystalloid preload. One of them had received enema for gastrointestinal surgery and was on preoperative angiotensin converting enzyme inhibitor, the other patient was on calcium channel and β-blocker combination. Preoperative hypovolemia, early fade of intubation response and preoperative antihypertensive medications could be the reasons for it.

10% of patients had self-limiting, rhythm disturbance in the form of ventricular bigeminy, ventricular premature beats and atrial ectopics during laryngoscopy and intubation which did not require any intervention. This is consistent with study of Ko SH[35] who reported 11% incidence of rhythm disturbance during laryngoscopy and intubation. We did not observe any episode of bronchospasm although some of the patients were smokers. Esmolol is a cardio-selective β-blocker with no action on bronchial smooth muscles and hence safe for use in smokers.[40]

The present study supports that hypertensives have exaggerated pressor response to laryngoscopy and tracheal intubation and are susceptible to post-intubation hypotension. There are certain limitations in the present study. Adrenaline and noradrenaline levels were not assayed during the study period which would have given the

measurement of effect of study drugs on stress response to laryngoscopy and tracheal intubation. Duration of observation of hemodynamic parameters beyond 7 minute post-intubation would have enabled to assess the duration of pressor response in hypertensives. This study was not powered to establish role of preoperative antihypertensive medications or influence of age of patient on pressor response to laryngoscopy and intubation hence future research powered to study effects of antihypertensive medications and effect of age on intubation response can be planned. We observed significant magnitude and incidence of post-intubation hypotension in Group EF, hence a future study designed by decreasing dose of both esmolol and fentanyl may help to evaluate the role of smaller dose of these drugs on intubation response.

CONCLUSION

Hypertensive patients exhibit exaggerated intubation response. Esmolol 1.5 mg/kg, alone or in combination with fentanyl 2 μg/kg given 2 minutes prior to laryngoscopy, attenuates the pressor response. Esmolol was more effective on heart rate response while the combination of esmolol and fentanyl was more effective on the arterial pressure; however, it caused significant post-intubation hypotension, hence should be used cautiously and on an individualized basis.

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