Original Article

Esmolol Compared with Fentanyl in Attenuating the Hemodynamic Response to Tracheal Intubation in Hypertensive Patients: A Randomized Controlled Study

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Background: Noxious stimuli caused by direct laryngoscopy and endotracheal intubation can produce tachycardia, arrhythmias, and hypertension. These responses are exaggerated in hypertensive patients.

Objective: To compare the effect of esmolol and fentanyl in attenuating the cardiovascular response after intubation in hypertensive patients.

Materials and Methods: The present study was a parallel randomised controlled trial done in a single center. One hundred hypertensive patients that underwent elective surgery requiring general anesthesia with endotracheal intubation were included. Patients were randomly divided into two groups, the esmolol group with 1.5 mg/kg intravenously and the fentanyl group with 2 µg/kg intravenously. Hemodynamic parameters were recorded at baseline, after study drug administration, at intubation, and 10 minutes thereafter. The primary outcomes were blood pressure and heart rate after intubation. Incidences of hypotension and bradycardia were secondary outcomes.

Results: Systolic blood pressure (SBP) after intubation was significantly lower in the fentanyl group than the esmolol group. SBP in the fentanyl group was 15.47 mmHg lower than the esmolol group. Diastolic blood pressure (DBP) in the fentanyl group was 6.96 mmHg lower than the esmolol group. Heart rate after intubation in the fentanyl and esmolol groups was not different. Hypotension was significantly more common in the fentanyl group compared with the esmolol group, while the incidence of bradycardia was not different between the groups.

Conclusion: Intravenous fentanyl 2 µg/kg was more effective at attenuating the blood pressure response to intubation in hypertensive patients than intravenous esmolol 1.5 mg/kg. However, fentanyl should be used cautiously due to the frequent occurrence of hypotension.

Keywords: Intubation; Hypertensive patients; Esmolol; Fentanyl; Heart rate; Blood pressure

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Laryngoscopy and endotracheal intubation during general anesthesia usually cause transient hypertension, tachycardia, and arrhythmia. These hemodynamic responses are likely to be more exaggerated in hypertensive patients than in normotensive patients. This magnification of the hemodynamic changes may be hazardous in hypertensive patients, leading to serious complications such as myocardial ischemia or intracerebral hemorrhage[1].

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Various methods and techniques have been used to attenuate hemodynamic responses to laryngoscopy and endotracheal intubation such as local anesthetics, opioids, calcium channel blockers, short acting beta-adrenergic blockers, and their combinations[2,3]. Esmolol and fentanyl can be used to reduce the hemodynamic response to endotracheal intubation. The optimal esmolol dose to attenuate the hemodynamic responses to endotracheal intubation has been studied[4,5]. A bolus dose of 2 mg/kg esmolol intravenously injected before induction has been found to be effective in blunting the cardiovascular response to laryngoscopy and intubation in normotensive and hypertensive patients[6-8]. However, Shailaja et al compared esmolol 1.5 mg/kg, the combination of esmolol 1.5 mg/kg, and fentanyl 2 µg/kg, and placebo in controlled hypertensive patients, and they found that esmolol 1.5 mg/kg and the combination of esmolol and fentanyl were effective in attenuating the cardiovascular response to intubation compared with placebo. However, significant hypotension occurred

more commonly in the combination group[9].

The aim of the present study was to compare the effect of esmolol 1.5 mg/kg and fentanyl 2 µg/kg in controlling the hemodynamic response during intubation in hypertensive patients. The primary outcomes were blood pressure and heart rate after intubation. The secondary outcomes were incidence of hypotension and bradycardia after administration of study drugs.

Materials and Methods

This parallel randomized controlled trial was reviewed and approved by the Institutional Review Board of Ramathibodi Hospital, Mahidol University, Thailand (Approval certificate ID: MURA 2018/145, Protocol ID 02-61-60). The study was conducted at a single medical school between September 2018 and December 2019. The present trial was registered at the Thaiclinicaltrials.org (Study ID: TCTR20200708003).

Patients

The authors included hypertensive patients, controlled by at least one oral antihypertensive agent, aged between 35 and 65 years scheduled for elective surgery under general anesthesia and required oral endotracheal intubation.

Patients with a history of cardiac disease, asthma/reactive airway disease, baseline heart rate less than 60 bpm, anticipated difficult airway, pregnancy, body mass index (BMI) of 30 kg/m² or more, American Society of Anesthesiologists (ASA) physical status of 3 or more, and those on beta-blockers were excluded from the study.

Randomization

Randomization was performed using a computer-generated block of four. Random allocation sequence was generated by research assistant. Each allocation sequences were concealed using closed envelopes technique. The patients were equally allocated into two groups, fentanyl (F) group and esmolol (E) group. Group E received esmolol 1.5 mg/kg while group F received fentanyl 2 µg/kg intravenously three to five minutes before intubation, respectively.

Intervention

All patients were evaluated and examined by an anesthesiology resident one day before surgery. Informed consent was obtained from each participant. All antihypertensive medications were continued until the morning of surgery except for diuretics. After the patient had been monitored in the operating theater, the concealed envelope was opened. A nurse anesthetist not involved in the present study prepared two syringes of medication and normal saline. The fentanyl and esmolol dosages were calculated and then prepared according to the allocation group. Each studied drug was diluted with normal saline up to 10 mL to mask the type of study drug. In fentanyl group, syringe A was fentanyl 2 µg/kg, which had been diluted to 10 mL, and syringe B was 10 mL of normal saline. In esmolol group, syringe A was 10 mL of normal saline and syringe B was esmolol 1.5 mg/kg, which had been diluted to 10 mL. Syringe A was given when preoxygenation with 100% O_2 was performed three minutes before anesthesia induction. Thereafter, anesthesia was induced using propofol target controlled infusion (TCI). The effective site target at 3 µg/mL was started. Target concentration can be titrated up 0.5 µg/mL incrementally if the eyelash reflex remained intact. After the ability to ventilate was ensured, atracurium 0.5 mg/kg and syringe B were administered. Direct laryngoscopy and tracheal intubation was performed three minutes after the administration of atracurium by second-year or third-year anesthesiology residents not aware of the randomized allocation.

Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure were collected at the following time points, before induction (baseline), one minute after propofol, and three minutes after atracurium administration, and immediately and 1, 3, 5, and 10 minutes after intubation. Complications including bradycardia or heart rate of less than 50 bpm, hypotension with a mean arterial pressure of less than 65 mmHg or a decrease of more than 20% from baseline, and arrhythmia were recorded. Depth of anesthesia was continuously maintained using propofol TCI for 10 minutes after tracheal intubation, and thereafter, anesthetic drugs and this technique were used at the discretion of the in-charge anesthesiologist.

Statistical analysis

The sample size was calculated to ensure 80% of power for detecting an expected 10% difference in SBP at maximum pressor response after tracheal intubation, which was determined from a prior study[8]. Twenty percent more subjects were added. The final total number of patients per group was 50.

All analyses were conducted on an intention to-treat basis. Data were described using the mean and standard deviation (SD) or the median and range as appropriate for continuous variables,

Table 1. Baseline characteristics and anesthetic related interventions between the esmolol and fentanyl groups

Characteristics	Esmolol (n=50)	Fentanyl (n=50)	p-value
Sex: male; n (%)	22 (44.0)	21 (42.0)	0.840
Age (years); mean [SD]	55.3 [6.6]	54.4 [6.0]	0.520
Weight (kg); mean [SD]	64.5 [8.0]	64.6 [9.5]	0.970
Height (cm), mean [SD]	161.7 [9.0]	162.0 [9.0]	0.860
BMI (kg/m^2); mean [SD]	24.6 [2.1]	24.5 [2.2]	0.780
ASA; n (%)			0.140
II	30 (60.0)	37 (74.0)	
III	20 (40.0)	13 (26.0)	
Diabetes mellitus; n (%)	12 (24.0)	12 (24.0)	1.000
Dyslipidemia; n (%)	15 (30.0)	12 (24.0)	0.500
Hemodynamic parameters before anesthesia induction; mean [SD]			
SBP (mmHg)	152.2 [15.4]	146.2 [19.2]	0.090
DBP (mmHg)	88.2 [9.5]	83.5 [11.1]	0.023
MAP (mmHg)	109.6 [10.2]	104.5 [12.4]	0.027
HR (bpm)	79.9 [7.7]	77.5 [8.7]	0.140
Propofol target effective site (μg/mL); mean [SD]	3.4 [0.4]	3.3 [0.3]	0.021
Intubation time (seconds); median (range)	30.0 (20.0 to 30.0)	30.0 (20.0 to 40.0)	0.290
Intubation attempt; n (%)			0.650
1	48 (96.0)	47 (94.0)	
2	2 (4.0)	3 (6.0)	

SD=standard deviation; BMI=body mass index; ASA=American Society of Anesthesiologists; SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; HR=heart rate

and the percentage for categorical variables. The corresponding data were compared between the esmolol and fentanyl groups using a t-test and a chi-square test or Fisher's exact test where appropriate. A multilevel mixed-effects linear regression was used to analyze the primary outcome with repeated measures after randomization. Statistical analyses were performed using Stata Statistical Software, version 17.1 (StataCorp LLC, College Station, TX, USA), with a significance threshold p-value of less than 0.05 (two-sided).

Results

The authors enrolled 152 patients. One hundred patients were randomized. All patients received intervention and all data were analyzed. The consort flow diagram was shown in Figure 1. There was no significant difference in the demographic data between the groups regarding gender, age, ASA physical status, weight, height, and BMI. SBP and heart rate before anesthesia induction were similar between both groups, but the DBP and mean arterial blood pressure were lower in the fentanyl group compared with the esmolol group. The target effective site concentration of propofol in the fentanyl group was lower than that in the esmolol group. Intubating

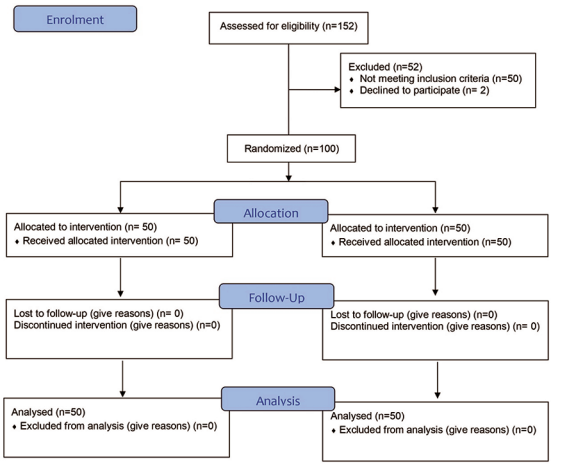

Figure 1. Consort flow diagram illustrating patient enrollment through analysis.

time and the number of intubation attempts were not different between groups. Comparison of baseline characteristics and anesthetic related interventions are presented in Table 1.

Hemodynamic parameters after intubation are shown in Table 2 and Figure 2. SBP and mean arterial blood pressure immediately and until 10 minutes after intubation in the fentanyl group were less than in the

Table 2. Hemodynamic parameters after intubation between the esmolol and fentanyl groups

Outcome	Esmolol; mean (SE)	Fentanyl; mean (SE)	Coefficient (95% CI)	p-value
SBP (mmHg)				
Immediate	153.98 (2.62)	141.96 (2.62)	12.02 (4.74 to 19.30)	0.001
1 minute	154.24 (2.62)	130.74 (2.62)	23.50 (16.23 to30.78)	<0.001
3 minutes	141.12 (2.62)	121.20 (2.62)	19.92 (12.65 to 27.20)	<0.001
5 minutes	130.86 (2.62)	114.38 (2.62)	16.48 (9.20 to 23.76)	<0.001
10 minutes	129.58 (2.62)	114.62 (2.62)	14.96 (7.68 to 22.24)	<0.001
DBP (mmHg)				
Immediate	92.30 (1.67)	87.90 (1.67)	4.40 (–0.23 to 9.03)	0.062
1 minute	92.92 (1.67)	81.18 (1.67)	11.74 (7.11 to 16.37)	<0.001
3 minutes	83.92 (1.67)	75.58 (1.67)	8.34 (3.71 to 13.00)	<0.001
5 minutes	77.40 (1.67)	69.98 (1.67)	7.42 (2.79 to 12.05)	0.002
10 minutes	77.28 (1.67)	72.16 (1.67)	5.12 (0.49 to 9.75)	0.030
MAP (mmHg)				
Immediate	112.54 (1.88)	105.94 (1.88)	6.60 (1.38 to 11.81)	0.013
1 minutes	113.32 (1.88)	97.78 (1.88)	15.54 (10.33 to 20.75)	<0.001
3 minutes	102.96 (1.88)	90.74 (1.88)	12.22 (7.01 to 17.43)	<0.001
5 minutes	95.16 (1.88)	84.80 (1.88)	10.36 (5.14 to 15.57)	<0.001
10 minutes	94.76 (1.88)	86.28 (1.88)	8.48 (3.27 to 13.69)	0.001
HR (bpm)				
Immediate	72.72 (1.31)	76.52 (1.31)	–4.64 (–8.27 to –1.01)	0.012
1 minutes	76.52 (1.31)	75.88 (1.31)	0.64 (–2.99 to 4.27)	0.730
3 minutes	75.24 (1.31)	74.74 (1.31)	0.50 (–3.13 to 4.13)	0.787
5 minutes	74.24 (1.31)	72.58 (1.31)	1.66 (–1.97 to 5.29)	0.370
10 minutes	75.88 (1.31)	72.34 (1.31)	3.54 (–0.09 to 7.17)	0.056

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; HR=heart rate; bpm=beats per minute; SE=standard error; CI=confidence interval

esmolol group. DBP in the patient in fentanyl group was significantly lower than in the esmolol group at 1, 3, 5, and 10 minutes after intubation. Heart rate in the fentanyl group was significantly higher compared with the esmolol group only immediately after intubation.

Multilevel mixed-effects linear regression showed that the overall SBP after intubation in the fentanyl group was 15.47 mmHg lower than in the esmolol group (95% confidence interval [CI] 10.11 to 20.82, p<0.001). Mean and SD of SBP were 128.2 mmHg and 24.5 mmHg in the fentanyl group and 143.7 mmHg and 18.5 mmHg in the esmolol group. A similar pattern was also seen in the overall diastolic and mean arterial pressure after intubation. In the fentanyl group, the overall diastolic and mean arterial pressure after intubation were 6.96 mmHg and 9.71 mmHg less than the esmolol group (95% CI 3.49 to 10.44, p<0.001; 95% CI 5.80 to 13.62 p<0.001, respectively). The mean and SD of the overall diastolic and mean arterial pressure was 78.4 (14.4) and 95.5 (17.2) mmHg in the fentanyl group and 83.3 (11.9) and 104.7 (13.1) mmHg in the esmolol group. However, there was no difference in the heart rate after intubation between the fentanyl and esmolol groups [mean (SD) 75.1 (10.9) and 75.8 (7.5), respectively; mean difference 0.96, 95% CI –2.11 to 3.5, p=0.628].

Table 3. Hemodynamic complications

Complications	Esmolol (n=50); n (%)	Fentanyl (n=50); n (%)	p-value
Hypotension	7 (14.0)	19 (38.0)	0.006
Bradycardia	0 (0.0)	2 (4.0)	0.150

The incidence of bradycardia and hypotension after intubation are shown in Table 3. All bradycardia events occurred without hypotension. There was no arrhythmia in any groups. Nine patients (18%) in the esmolol group and four patients (8%) in the fentanyl group had SBP greater than 180 mmHg or a mean arterial blood pressure of greater than 120 mmHg after intubation (p=0.14).

Discussion

The authors performed the present study to

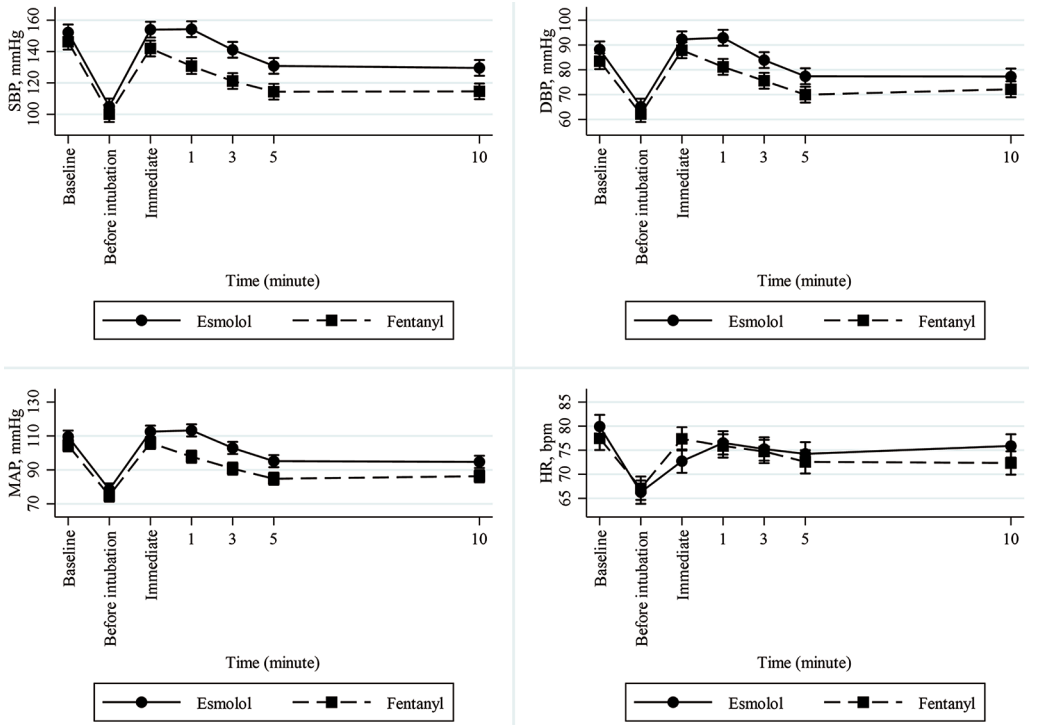

Figure 2. Hemodynamic parameters in the esmolol and fentanyl groups during baseline, before intubation, 1, 3, 5, and 10 minutes after intubation.

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; HR=heart rate

compare the effectiveness of fentanyl and esmolol in blunting the hemodynamic response after intubation in treated hypertensive patients. The main findings of the present study are as follows, 1) fentanyl 2 µg/kg decreased blood pressure after intubation to a greater extent than esmolol 1.5 mg/kg, 2) heart rate after intubation was not different between the groups, and 3) incidence of hypotension was more common in the fentanyl group compared with the esmolol group.

Varma et al's study showed that esmolol 2 mg/kg was more effective than fentanyl 2 µg/kg in attenuating the sympathetic response to intubation[7]. This is inconsistent with the present study, which showed that the increase in blood pressure in the esmolol group was higher than that in the fentanyl group. This may be because of the lower esmolol dose used in the present study and the longer duration between fentanyl administration and intubation in the present study. Sharma et al[10] and Figueredo et al[11] demonstrated that the effect of esmolol on suppressing the hemodynamic response to intubation is dose-dependent. The lower dose effectively controlled only the heart rate response while the higher dose attenuated both the heart rate and blood pressure response. In the present study, fentanyl was administered five minutes before intubation while Varma et al administered fentanyl three minutes before laryngoscopy[7]. Ko et al examined the optimal fentanyl injection time, and they found that the most effective time to administer fentanyl to protect circulatory responses to laryngoscopy was five minutes before tracheal intubation[12].

Esmolol is an ultra-short acting beta-1 selective adrenergic blocker with very rapid onset and offset of action. Esmolol has been used in different doses bolus to prevent sympathetic response to laryngoscopy and tracheal intubation. Yuan et al[13] and Parnass et al[14] reported that single bolus dose of esmolol 100 and 200 mg could effectively prevent the tachycardia and hypertension produced by laryngoscopy and intubation. The previous studies by Gupta et al[6] Varma et al[7], and Louizos et al[15] showed that esmolol 2 mg/kg was effective in attenuating the hemodynamic response to intubation. Shailaja et al[9], Ugur et al[16], Singhal et al[17], and Mulimani et al[18] demonstrated that esmolol 1.5 mg could prevent tachycardia and hypertension after intubation. In the present study, the authors selected an esmolol dose of 1.5 mg/kg to avoid decreasing the blood pressure and heart rate more than necessary, which may be harmful

in hypertensive patients. The authors administered esmolol three minutes before intubation because that was optimal effective time[16].

Overall complications were less common in the esmolol group than in the fentanyl group. This may be because of the effect of the esmolol dose that was used, as described earlier, and esmolol's ultra-short duration of action. Its elimination half-life is approximately nine minutes[19]. A continuous propofol drip may contribute to and synergize with fentanyl's hypotensive effect[20].

The present study has strengths. It was designed to observe drug efficacy by eliminating the timing effect. The authors selected the optimal injection time for both drugs. Propofol TCI was used to provide an adequate depth of anesthesia. Limitations of the present study were the patients were intubated by second and third-year residents having differences in their skills and experience with intubation. The sympathetic response to intubation may vary with the degree of stimuli. The catecholamine level was not examined in the present study.

Conclusion

Intravenous fentanyl 2 µg/kg was more effective in attenuating the blood pressure response to laryngoscopy and endotracheal intubation in hypertensive patients than intravenous esmolol 1.5 mg/kg. However, hypotension after intubation should be monitored and promptly treated when fentanyl was administered to reduce the hemodynamic response after intubation.

What is already known on this topic?

Various methods and techniques have been used to attenuate hemodynamic responses to laryngoscopy and endotracheal intubation such as local anesthetics, opioids, calcium channel blockers, short acting beta-adrenergic blockers, and their combinations. Fentanyl 2 mcg/kg has been used to blunt hemodynamic responses to laryngoscopy in normotensive and hypertensive patient for a very long time. Esmolol 1.5 mg/kg has also been used to blunt hemodynamic responses in normotensive patient.

What this study adds?

This study compares effectiveness of esmolol 1.5 mg/kg to the commonly used drug fentanyl 2 mcg/kg in blunting hemodynamic responses to laryngoscopy in hypertensive patient. Incidence of hypotension and bradycardia was record and compared between groups. This study showed that fentanyl 2 mcg/kg was more effective in attenuating hemodynamic response to laryngoscopy but associated with more hypotensive episodes.

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Conflicts of interest

The authors declare that they have no competing interests.

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