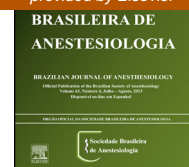




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## SCIENTIFIC ARTICLE

# Comparison of bolus and continuous infusion of esmolol on hemodynamic response to laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft

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### KEYWORDS

Esmolol;  
Laryngoscopy;  
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intubation;  
Sternotomy  
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Coronary artery;  
Bypass graft surgery

### Abstract

**Background and objective:** The aim of this randomized, prospective and double blinded study is to investigate effects of different esmolol use on hemodynamic response of laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft surgery.

**Methods:** After approval of local ethics committee and patients' written informed consent, 45 patients were randomized into three groups equally. In Infusion Group; from 10 min before intubation up to 5th minute after sternotomy, 0.5 mg/kg/min esmolol infusion, in Bolus Group; 2 min before intubation and sternotomy 1.5 mg/kg esmolol IV bolus and in Control Group; %0.9 NaCl was administered. All demographic parameters were recorded. Heart rate and blood pressure were recorded before infusion up to anesthesia induction in every minute, during endotracheal intubation, every minute for 10 minutes after endotracheal intubation and before, during and after sternotomy at first and fifth minutes.

**Results:** While area under curve (AUC) ( $SAP \times \text{time}$ ) was being found more in Group B and C than Group I, AUC ( $SAP \times T_{\text{int}}$  and  $T_{\text{st}}$ ) and AUC ( $SAP \times T_2$ ) was found more in Group B and C than Group I ( $p < 0.05$ ). Moreover AUC ( $HR \times T_{\text{st}}$ ) was found less in Group B than Group C but no significant difference was found between Group B and Group I.

**Conclusion:** This study highlights that esmolol infusion is more effective than esmolol bolus administration on controlling systolic arterial pressure during endotracheal intubation and sternotomy in CABG surgery.

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**PALAVRAS-CHAVE**

Esmolol;  
Laringoscopia;  
Intubação  
endotraqueal;  
Hemodinâmica em  
esternotomia;  
Artéria coronária;  
Cirurgia de  
revascularização

## Comparação de esmolol em *bolus* e infusão contínua na resposta hemodinâmica à laringoscopia, intubação orotraqueal e esternotomia em cirurgia de revascularização coronária

**Resumo**

*Justificativa e objetivo:* o objetivo deste estudo prospectivo, randômico e duplo-cego foi investigar os efeitos do uso diferente de esmolol na resposta hemodinâmica à laringoscopia, intubação orotraqueal e esternotomia em cirurgia de revascularização coronária.

*Métodos:* após obter a aprovação do Comitê de Ética local e consentimento informado assinado pelos pacientes, 45 pacientes foram randomicamente divididos em três grupos. O Grupo I (infusão) recebeu 0,5 mg/kg/min de esmolol em infusão a partir de 10 min antes da intubação até 5 minutos após a esternotomia; o Grupo B (*bolus*) recebeu 1,5 mg/kg de esmolol em *bolus* IV a partir de 2 min antes da intubação e esternotomia; o grupo C (controle) recebeu NaCl a 0,9%. Todos os parâmetros demográficos foram registrados. Os valores de frequência cardíaca e pressão arterial foram registrados desde antes da infusão até a indução da anestesia a cada minuto, durante a intubação endotraqueal, a cada minuto durante 10 min após a intubação endotraqueal e antes, durante e após a esternotomia no primeiro e quinto minutos.

*Resultados:* enquanto a área sob a curva (ASC) ( $SAP \times tempo$ ) foi maior nos grupos B e C que no Grupo I, a ASC ( $SAP \times T_{int}$  e  $T_{st}$ ) e ASC ( $SAP \times T_2$ ) foram maiores nos grupos B e C que no Grupo I ( $p < 0,05$ ). Além disso, a ASC ( $FC \times T_{st}$ ) foi menor no Grupo B que no Grupo C, mas não houve diferença significativa entre os grupos B e I.

*Conclusão:* este estudo destaca que a administração de esmolol em infusão é mais eficaz que em *bolus* para controlar a pressão arterial sistólica durante a intubação endotraqueal e esternotomia em CRC.

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**Introduction**

Patients undergoing coronary artery bypass graft (CABG) surgery are at risk for perioperative myocardial ischemia. Tachycardia as a predictor for increased myocardial oxygen consumption which doubles the incidence of myocardial ischemia. During the operative procedure for coronary revascularization, some maneuvers, such as intubation, sternotomy and mediastinal preparation, may be associated with tachycardia and increases in blood pressure despite the adequate level of anesthesia.<sup>1</sup>

Some drugs (IV opioids, vasodilators, calcium channel and  $\beta$ -blockers) are available for the clinicians to control the hemodynamic response to laryngoscopy and intubation.<sup>2</sup>  $\beta$ -adrenoceptor blockers were shown to decrease the incidence of postoperative myocardial ischemia.<sup>3</sup>

Esmolol (metil-3[4-(2-hidroxy-3[izopropylamino]propoxy)fenil]) is a specific cardioselective beta 1-blocker and it is hydrosoluble, without intrinsic sympathetic activity or membrane stabilizing activity at therapeutic dosages. Distribution and elimination half-life is 2 and 9 min, respectively. Esmolol is hydrolyzed by the blood esterases and a suitable agent for the perioperative period.<sup>4</sup>

Esmolol as a bolus or infusion was shown to prevent tachycardia and hypertension during laryngoscopy and intubation in a meta-analysis and previous studies.<sup>5-7</sup>

So far, esmolol bolus and infusion administration has not been previously compared in cardiac patients. The purpose of this randomized, prospective, double blinded study, was to evaluate the effect of 1.5 mg/kg esmolol bolus and 0.5 mg/kg/min esmolol infusion on hemodynamic response

of laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft (CABG) surgery.

**Methods**

Forty five patients, aging between 18 and 80 years, ejection fraction >40%, in ASA II–IV status, scheduled for elective CABG surgery, between February and April 2006, in Ankara University Medical Faculty were enrolled to the study after obtaining approval from the Local Research Ethics Committee and written informed consent. Patients with asthma, first-degree atrioventricular block, heart rate <50 beats/min, acute myocardial infarction, Mallampati score more than two and under  $\beta$ -blocker treatment or contraindicated for  $\beta$ -blocker agent were excluded from the study.

One hour before the operation, patients were premedicated with 2.5 mg diazepam and 50 mg dolantine IM. Preoperative medical treatments were continued till the morning of the operation. Patients' age, gender, weight, height, chronic diseases and medications were recorded as demographic parameters. Upon their arrival to the operating room patients were monitored by pulse oximetry, electrocardiogram and non-invasive arterial blood pressure. An intravenous line was inserted with 18 gauge catheter and % 0.9 NaCl infusion was started, 0.04 mg/kg midazolam IV was administered. For invasive blood pressure monitoring, an intraarterial catheter was inserted into the left radial artery after local anesthetic infiltration. Sixty seconds after induction of general anesthesia with 0.3 mg/kg

ethomidate, 5 µg/kg fentanyl vs. 0.1 mg/kg vecuronium patients were intubated by the same clinician who were blind to the study drugs. Anesthesia was maintained with 3 µg/kg fentanyl and 0.01 mg/kg midazolam IV bolus injection every 30 min. Patients were ventilated to normocapnie with 50% air-oxygen in approximately 0.5 MAC isoflurane. 0.03 mg/kg vecuronium IV was administered as needed. Patients were randomly assigned according to computer-generated random number sequence into one of three groups. In Infusion Group (Group I); 0.5 mg/kg/min esmolol infusion was started 10 min before the endotracheal intubation up to 5th minute after sternotomy, and 2 min before both intubation and sternotomy %0.9 NaCl was administered, in Bolus Group (Group B); 2 min before both endotracheal intubation and sternotomy 1.5 mg/kg esmolol bolus IV and from 10 min before endotracheal intubation up to 5th minute after sternotomy %0.9 NaCl was administered and in Control Group (Group C); %0.9 NaCl infusion and bolus was administered instead of esmolol. Heart rate (HR) and systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were recorded before infusion (baseline) up to anesthesia induction, during and soon after anesthesia induction, during endotracheal intubation, every minute for 10 min after endotracheal intubation and before, during and at first and fifth minutes after sternotomy. All demographic parameters were recorded.

SPSS 10.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all data analyses. For  $\alpha=0.05$  and  $\beta=0.20$ , sample size was calculated 15 subjects for each groups. ANOVA and Chi-square tests were used for analysis of demographic variables. Area under curve (AUC) (heart rate, systolic, diastolic and mean arterial pressure  $\times$  time) was calculated and compared with one-way ANOVA test between groups. A  $p$  value of  $<0.05$  was considered statistically significant.

## Results

No significant difference was found between groups according to demographic parameters (Table 1).

AUC (heart rate, systolic, diastolic and mean arterial pressure  $\times$  time) between groups were compared and according to Table 2, Group I was significantly more effective than other two groups in controlling systolic arterial pressure (SAP) but no significant difference on other parameters was found.

AUC (heart rate, systolic, diastolic and mean arterial pressure  $\times T_1$  (time between the beginning of infusion and the beginning of anesthesia induction) and  $T_2$  (time between the beginning of anesthesia induction and the 5th minute after sternotomy)) were compared. According to Table 3 infusion group was significantly more effective than other two groups in controlling SAP after induction but no significant difference was observed on other parameters.

AUC (heart rate, systolic, diastolic and mean arterial pressure  $\times T_{\text{int}}$  (time from endotracheal intubation to sternotomy) and  $T_{\text{st}}$  (time from beginning of sternotomy to 5th min after sternotomy) were compared. According to Table 4, infusion group was significantly more effective than other two groups on controlling SAP during sternotomy and intubation. Moreover bolus group was significantly more effective than control group in controlling heart rate (HR) during ster-

notomy but no significant difference was observed between infusion and bolus group.

No adverse or side effects were recorded in both groups.

## Discussion

This prospective, randomized, double blinded trial was designed to determine the hemodynamic effects of different use of esmolol during laryngoscopy, intubation and sternotomy in CABG surgeries and as a result of this study we found out that while esmolol infusion was significantly more effective than esmolol bolus on controlling SAP during both intubation and sternotomy, esmolol bolus was significantly more effective on controlling HR only during sternotomy when compared to control group but no significant difference was found when compared to infusion group. No significant side effects were observed.

Cardiovascular changes such as hypertension and tachycardia during tracheal intubation are potentially detrimental to patients with ischemic heart disease. Esmolol is the  $\beta$ -selective adrenergic blocker available and with its rapid onset and extremely short duration of action, would appear to be an ideal drug for preventing acute increases in HR and SAP.<sup>8</sup>

However, we would advise caution when using bolus and infusion doses of esmolol but no patient in our study required treatment for hypotension, bradycardia, or significant arrhythmias. No side effects were observed in any group of patients.

Since esmolol has been used clinically, its infusion use before CABG surgery or other procedures for preventing cardiac ischemia was studied and shown to be effective.<sup>9</sup> As clinical use of esmolol became more common, due to its short acting, simple and effective bolus use of esmolol had increased.<sup>10-14</sup>

According to our knowledge, the bolus and infusion administration of esmolol has not been compared before in a previous study, so we decided to design this study.

As an optimal intravenous (IV) esmolol dose for use during anesthesia induction (laryngoscopy and intubation) and emergence (extubation) has been previously determined to be 1.5 mg/kg, we used the same bolus dose in our study.<sup>15-16</sup> As we could not find an optimal infusion dose of esmolol we used an average infusion dose that was 0.5 mg/kg/min in our study.<sup>17</sup> While Parnass et al.<sup>13</sup> were found no difference between 100 and 200 mg esmolol on controlling hemodynamic response during intubation, Yuan et al.<sup>12</sup> found out that 200 mg esmolol presented a better hemodynamic stability than 100 mg esmolol during induction of anesthesia in their study. Moreover, in another multicenter study, while IV bolus administration of 100 mg esmolol was being shown to be effective in controlling hemodynamic response of endotracheal intubation, 200 mg dosage was shown to cause more hypotension without desired effect.<sup>18</sup>

These controversial results indicated that other factors such as patients' medications, other diseases, ASA status, ages, intubation difficulties, different Mallampati scores might have affected the results and it is very important to standardize the patients' characteristics with even the clinicians who attempt to intubate. That is why in our study, patients were intubated by the same clinician who was

**Table 1** Demographic data of groups.

	Group I (n = 15)	Group B (n = 15)	Group C (n = 15)	p
Age (years)	61 ± 6	63 ± 7	64 ± 7	NS
Gender (M/F)	10/5	11/4	10/5	NS
Weight (kg)	84 ± 12	87 ± 10	81 ± 15	NS
Height (cm)	171 ± 6	175 ± 8	172 ± 9	NS
ASA Classification (I/II/III/IV)	0/1/14/0	0/2/13/0	0/3/12/0	NS
Chronic Disease (±)	15/0	15/0	15/0	NS
Medication (±)	15/0	15/0	15/0	NS

Data is presented as mean ± SD.

Group I: Esmolol infusion group Group B: Esmolol bolus group Group C: Control group; NS: Statistically not significant.

**Table 2** Area under curve (AUC) of groups. (HR, SAP, DAP and MAP × T).

	Group I (n = 15)	Group B (n = 15)	Group C (n = 15)
HRXTIME (cm <sup>2</sup> )	1729 ± 208	1893 ± 304	1973 ± 304
SAPXTIME(cm <sup>2</sup> )	2843 ± 360*	3297 ± 548	3151 ± 397
DAPXTIME(cm <sup>2</sup> )	1635 ± 364	1767 ± 348	1650 ± 304
MAPXTIME(cm <sup>2</sup> )	2189 ± 366	2404 ± 399	2225 ± 293

Data is presented as mean ± SD.

HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; T, time; Group I, Esmolol infusion group; Group B, Esmolol bolus group Group C, control group.

\* p < 0.05 compared with Group B and C.

**Table 3** Area under curve (AUC) of groups. (HR, SAP, DAP and MAP × T<sub>1</sub> and T<sub>2</sub>).

	Group I (n = 15)	Group B (n = 15)	Group C (n = 15)
HRxT <sub>1</sub> (cm <sup>2</sup> )	743 ± 91	861 ± 167	835 ± 153
HRxT <sub>2</sub> (cm <sup>2</sup> )	986 ± 136	1032 ± 150	1136 ± 224
SAPxT <sub>1</sub> (cm <sup>2</sup> )	1329 ± 215	1456 ± 298	1408 ± 252
SAPxT <sub>2</sub> (cm <sup>2</sup> )	1514 ± 193*	1840 ± 299	1743 ± 224
DAPxT <sub>1</sub> (cm <sup>2</sup> )	661 ± 143	706 ± 161	669 ± 113
DAPxT <sub>2</sub> (cm <sup>2</sup> )	973 ± 275	1061 ± 223	981 ± 211
MAPxT <sub>1</sub> (cm <sup>2</sup> )	989 ± 161	1070 ± 199	973 ± 146
MAPxT <sub>2</sub> (cm <sup>2</sup> )	1200 ± 265	1334 ± 259	1251 ± 191

Data is presented as mean ± SD.

HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; T<sub>1</sub>, time between the beginning of infusion and the beginning of anesthesia induction; T<sub>2</sub>, time between the beginning of anesthesia induction and the 5th minute after sternotomy; Group I, Esmolol infusion group; Group B, Esmolol bolus group; Group C, Control group.

\* p < 0.05 compared with Group B and C.

**Table 4** AUC (HR, SAP, DAP and MAP × T<sub>int</sub> and T<sub>st</sub>) of groups.

	Group I (n = 15)	Group B (n = 15)	Group C (n = 15)
HR × T <sub>int</sub> (cm <sup>2</sup> )	797 ± 114	853 ± 135	925 ± 189
HR × T <sub>st</sub> (cm <sup>2</sup> )	188 ± 29	179 ± 33**	212 ± 40
SAP × T <sub>int</sub> (cm <sup>2</sup> )	1218 ± 157*	1486 ± 254	1368 ± 185
SAP × T <sub>st</sub> (cm <sup>2</sup> )	296 ± 51*	354 ± 67	374 ± 60
DAP × T <sub>int</sub> (cm <sup>2</sup> )	726 ± 103	857 ± 192	777 ± 170
DAP × T <sub>st</sub> (cm <sup>2</sup> )	246 ± 207	203 ± 45	203 ± 50
MAP × T <sub>int</sub> (cm <sup>2</sup> )	968 ± 249	1078 ± 222	981 ± 154
MAP × T <sub>st</sub> (cm <sup>2</sup> )	231 ± 33	255 ± 52	169 ± 51

Data is presented as mean ± SD.

HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; T<sub>int</sub>, time from endotracheal intubation to sternotomy; T<sub>st</sub>, time from beginning of sternotomy to 5th minute after sternotomy; Group I, Esmolol infusion group; Group B, Esmolol bolus group; Group C, control group.

\* p < 0.05 compared with Group B and C.

\*\* p < 0.05 compared with Group C.

blind to the study drug, to standardize the noxious stimuli during laryngoscopy and intubation. Moreover patients' medications and Mallampati scores were similar between groups.

In some previous studies patients were included into the study according to their medications with or without  $\beta$ -blocker agents.<sup>17,19</sup> The results of these studies revealed that patients who enrolled to these studies should have been chosen upon their treatment of  $\beta$ -blocker agents. In our study the patients on  $\beta$ -blocker agents were not included as similar to Korenaga et al's study. They excluded patients on  $\beta$ -blocker therapy from their study and reported a slight but statistically insignificant decrease in heart rate from 83 to 70 beat/min during infusion of esmolol 500  $\mu$ g/kg/min prior to anesthetic induction.<sup>17</sup> The same dose was used in our study and we also did not observe any significant decrease in HR.

But unlike our study, Brujin et al<sup>19</sup> investigated the hemodynamic effects of esmolol in chronically  $\beta$ -blocked patients undergoing coronary artery bypass surgery and they concluded that in patients whom chronic  $\beta$ -blocker therapy was continued until the time of surgery, esmolol did not further attenuate the heart rate response but did attenuate the increase in blood pressure.

There are different doses of esmolol studied in previous studies and the choice of optimal dose of esmolol is very important to balance between the desired and side effects. Although we preferred 1.5 mg/kg bolus dose of esmolol and many studies showed the effectiveness of large doses of esmolol, Bensky et al.<sup>20</sup> compared 0.2 and 0.4 mg/kg esmolol and found out that both doses were more effective in decreasing the heart rate than control group and the 0.4 mg/kg dose significantly blunted the increase in mean arterial pressure seen in control group.

However, in another study,<sup>21</sup> the result of a combination of nicardipine (30  $\mu$ g/kg) and esmolol (1 mg/kg) showed no significant change in hemodynamic response to tracheal intubation when compared to saline.

There are also different techniques to find out the best one in previous studies. Some clinicians investigated the effect of esmolol bolus followed by esmolol infusion on hemodynamic effects to find out the most proper dose of esmolol.<sup>11,22-26</sup> In a study made by Schäffer et al., double bolus of esmolol was used instead of one bolus to control the hemodynamic effect and they reached a better result with double bolus of 100 mg esmolol.<sup>27</sup> In another previous studies,<sup>28-37</sup> esmolol was compared with other agents alone or as combination.

These techniques and different doses of esmolol should be studied to use alone or in combination to find out the most appropriate one. However, it should be kept in mind that the patient characteristics and different procedures may affect the effects of Esmolol and other drugs.

There are some limitations of this current study. We did not calculate PCWP and cardiac index in our study. Those parameters would be a better guide for cardiac performance. We did not measure catecholamine levels of patients which would take us to more reliable results about the hemodynamic and stress response. Moreover the sample size of the study disabled us to demonstrate other factors that might enroll to the changes for hemodynamic parameters. As bolus dose was not as effective as on blood pressure, it

might have been better to add another bolus dose group or make double boluses to investigate the effectiveness as the previous studies.

In conclusion, according to our study that the effect of esmolol bolus and infusion administration on hemodynamic response to laryngoscopy, endotracheal intubation and sternotomy in CABG surgery was compared, both groups were found safe and esmolol infusion was found more effective than esmolol bolus on controlling SAP during both intubation and sternotomy.

## Conflicts of interest

The authors declare no conflicts of interest.

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