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Original article

EFFECT OF ESMOLOL CARDIOPLEGIA ON INOTROPIC SUPPORT AND INOTROPIC SCORE AFTER CORONARY ARTERY BYPASS SURGERY

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Abstract

Coronary artery bypass surgery is associated with numerous complications as a result of perioperative myocardial ischemia. Administration of esmolol as an adjunct to cardioplegia is a pharmacological cardioprotective method to protect the myocardium in patients with coronary artery disease.

The aim of this study was to determine whether the application of esmolol as an adjunct to cardioplegia itself would provide additional myocardial protection, reduce the need for inotropic and vasopressor support, and decrease the inotropic score.

A total of 100 patients aged 40-80 years with coronary artery disease were included in this prospective, randomized, controlled study. Patients were grouped into two randomized groups according to whether they received esmolol in line with a well-defined protocol or placebo. In all patients, a vasoactive inotropic score was calculated by a formula.

The inotropic score in the operating room was statistically insignificant (p=0.141), and the highest inotropic score in the first 24 hours was statistically significantly lower (p= 0.002) in patients receiving esmolol compared to others. Inotropic support in intensive care unit with statistical significance (p=0.0001) and vasopressor support with borderline significance (p=0.06) was applied in a lower percentage after 24 hours in patients given esmolol.

A pharmacological cardioprotective method to protect the myocardium with esmolol in patients with coronary artery disease has a positive effect in reducing the inotropic score, respectively less use of inotropic and vasopressor support after coronary artery bypass surgery.

Keywords: esmolol, coronary artery disease, cardiac surgery, cardioanesthesia, inotropic score

Introduction

Coronary artery bypass surgery (CABG) is associated with numerous complications as a result of perioperative ischemia of the myocardium and numerous cardioplegic solutions are used for the protection of the myocardium (myocardial protection) during cardiopulmonary bypass, all aimed at reducing or preventing perioperative infarction and/or post-ischemic ventricular dysfunction. In most cases, complications are due to ischemic-reperfusion injury and inadequate

protection of the myocardium. Therefore, there is a need to develop better methods to protect the heart during surgery[1-7].

Administration of BBs belongs to pharmacological cardioprotective methods for protection of the myocardium, which includes use of a cardioprotective agent before aortic clamping, adding a pharmacological agent to the cardioplegic solution, or administration of a cardioprotective agent at the time of removal of the aortic clamp or a combination of all these different approaches[5-12].

Esmolol is an ultra-short-acting BB that represents a cardioselective BB, with a half-life of about 9 minutes due to esterase hydrolysis, which allows its negative inotropic effect to be quickly terminated after the infusion is reduced or stopped[13-28].

Material and methods

This prospective, randomized, controlled study included 100 patients aged 40-80 years with coronary artery disease that, according to the recommendations of professional associations[29], refers to revascularization with CABG. All patients met the criteria for inclusion in the study and had signed an informed written consent for their participation in the study, which was previously explained to them in detail.

Patients were randomized into two groups depending on whether they received esmolol-beta1-selective adrenergic blocker or placebo. A computer-generated list of random numbers was used for appropriate randomization of patients. Patients were assigned a progressive randomization number that was written on a sealed, numbered, opaque envelope containing information about patient allocation (esmolol or placebo).

Inclusion criteria:

- Patients diagnosed with CAD, with left ventricular ejection fraction (LVEF) < 50% or left ventricular end-diastolic dimension determined by echocardiography (LVEDD) > 60 mm, indicated for surgical revascularization - CAD, according to the latest recommendations of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS)[29].
- Patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) who were not suitable for percutaneous coronary intervention (PCI), and were indicated for CABG only after stabilization of the general condition and normalization of cardiac biomarkers.
- Patients with CAD who, due to the severity of the angiographic finding of the coronary arteries, left main coronary artery disease or its equivalent, had to be revascularized during the same hospitalization.

Exclusion criteria:

- Patients in whom urgent surgical revascularization (emergency, salvage) was indicated (24). This included patients with STEMI, NSTEMI who had prolonged ischemia, pulmonary edema refractory to medical treatment, cardiogenic shock, that is, all conditions that required immediate surgical intervention due to a life-threatening condition.
- Patients who required concomitant cardiac surgery (valvular surgery and aortic surgery).
- Patients requiring any form of perioperative mechanical circulatory support.
- Re-do ("Re-do") CABG.

- Patients who had an allergic reaction to esmolol.
- Patients participating in another randomized trial.

Methods

According to the protocol for the inclusion of esmolol:

The first dose of esmolol (1 mg/kg in 10 mg/ml solution) was administered through a central venous catheter after cannulation of the aorta, i.e., immediately before clamping the aorta.

A second dose of esmolol (2 mg/kg in a 10 mg/ml solution) was given along with antegrade cold blood cardioplegia. The maximum dose of esmolol given before aortic clamping was 100 mg, while the maximum dose of esmolol given with cardioplegia was 200 mg.

The control group of subjects received a placebo (saline solution) in the same volume.

Vasoactive inotropic score (VIS) was calculated for each patient according to the following formula: (Dobutamine dose (μg/kg/min) + Dopamine dose (μg/kg/min) + Epinephrine dose (μg/kg/min x100) + Norepinephrine (μg/kg/min x100) ++ Enoximone dose (μg/kg/ min) during the operation itself, as well as in the postoperative period[31,32,33,34].

The following parameters were monitored in all patients included in the study: (1) inotropic score in the operating room; (2) highest inotropic score in the first 24 hours; (3) inotropic support on the way out from the operating room; (4) duration of inotropic support in the ICU; (5) duration of vasopressor support in ICU; (6) highest dose of epinephrine in the first 24 hours; (7) highest dose of norepinephrine in the first 24 hours. Also (8), all patients were monitored for serum lactate concentration during the first 3 hours in ICU.

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as mean ± standard deviation. Differences between groups were tested using Pearson's Chi-square test for categorical variables and Mann-Whitney non-parametric tests for continuous variables. Correlation was done using Pearson's or Spearman's analyses. All data analyses were performed using the SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois, USA), and $p \leq 0.05$ was considered statistically significant.

Results

The comparison of the basal values of patients divided into two groups of 50 patients each: those who received the fast-acting beta-1 selective adrenergic blocker - esmolol and those without it are given in Tables 1 and 2.

Patients in both groups were almost identical in age (p=0.471), with a slight predilection of females in the esmolol group; patients in both groups were almost identical in increased body weight (p=0.398), and in terms of clinical classifications (NYHA and CCS class), as well as surgical scores (EuroSCORE and STS score), patients in the esmolol group had insignificantly lower values, that is, more favorable clinical and pre-surgical performance (Table 1, Figure 1).

Regarding risk factors for atherosclerosis (Table 2), there was no statistically significant difference in their representation in patients with and without given esmolol.

Table 1. Comparison of anthropometric measurements and clinical scores for pre-surgical performance of patients divided into those with and without given esmolol

Parameters	With esmolol n=50	Without esmolol n=50	p
Age (y)	65.18±7.83	65.96±9.30	0.471
Sex Men/Women (%)	70/30	84/16	0.077
BMI (kg/m2)	27.45±4.58	28.06±4.34	0.398
NYHA classification	2.96±0.57	3.16±0.68	0.105
CCS classification	2.94±0.58	3.18±0.69	0.059
EuroSCORE	4.99±3.99	5.35±4.34	0.850
STS score	1.91±1.81	2.28±2.50	0.491

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS score = Society of Thoracic Surgeons score

Table 2. Comparison of risk factors in patients divided into those with and without given esmolol

Parameters	With esmolol n=50	Without esmolol n=50	p
Smoking (%)	70	68	0.500
Hypertension (%)	90	88	0.500
Dyslipidemia (%)	84	86	0.500
Diabetes mellitus (%)	56	58	0.500
COPD (%)	16	10	0.277
Previous PCI (%)	22	16	0.306
CHF (%)	-	2.0	0.500
PAD (%)	12	20	0.207
CVI (%)	6	10	0.357
Previous AF (%)	2	4	0.500
CRF (%)	2	12	0.056
Carotid disease (%)	18	18	0.602

BMI = body mass index; AF = atrial fibrillation; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVI = cerebrovascular insult

The comparison of the need for inotropic and vasopressor perioperative and postoperative support in both groups of patients, that is, the value of the inotropic score in the operating room and in the first 24 hours is given in Table 3.

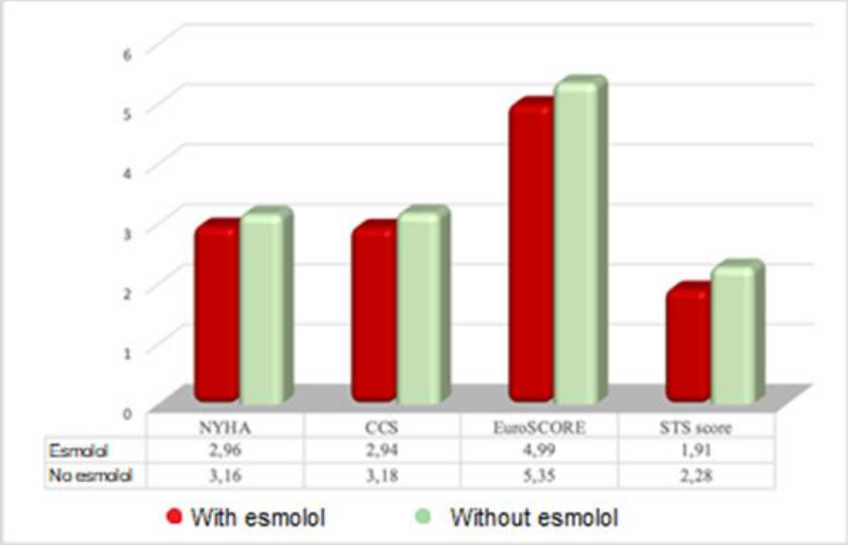

Fig. 1. Comparison of score value in patients with and without esmolol

Table 3. Comparison of perioperative and postoperative characteristics in patients divided into those with and without given esmolol

Parameters	**With esmolol n=50**	**Without esmolol n=50**	**p**
Inotropic score in the operating room	6.15±5.26	8.61±7.10	0.141
Highest inotropic score in the first 24 hours	7.39±5.62	11.94±8.44	0.002
Inotropic support on the way out from the operating room (%)	84	86	0.500
Inotropic support in ICU (%)			
No support	12	10	0.0001
First 24 h	70	24	
>24 h	18	66	
Vasopressor support (%)			
No support	12	14	0.066
First 24 h	76	56	
>24 h	12	30	
Highest dose of epinephrine in the first 24 hours (mcg/kg/min)	0.02±0.01	0.03±0.02	0.001
Highest dose of norepinephrine in the first 24 hours (mcg/kg/min)	0.095±0.27	0.088±0.07	0.025
Serum lactate concentration during the first 3 hours (mmol/L)	2.29±1.15	3.41±3.69	0.020

Moreover, the inotropic score in the operating room was 6.15±5.26 in the esmolol group compared to 8.61±7.10 in the control group (p=0.141), and the highest inotropic score in the first 24 hours was 7.39± 5.62 in the studied esmolol group compared to 11.94±8.44 in patients in the

control placebo group (p=0.002) (Table 3, Figure 2), while the percentage representation of inotropes on the way out of the operating room was almost identically distributed in both groups of patients.

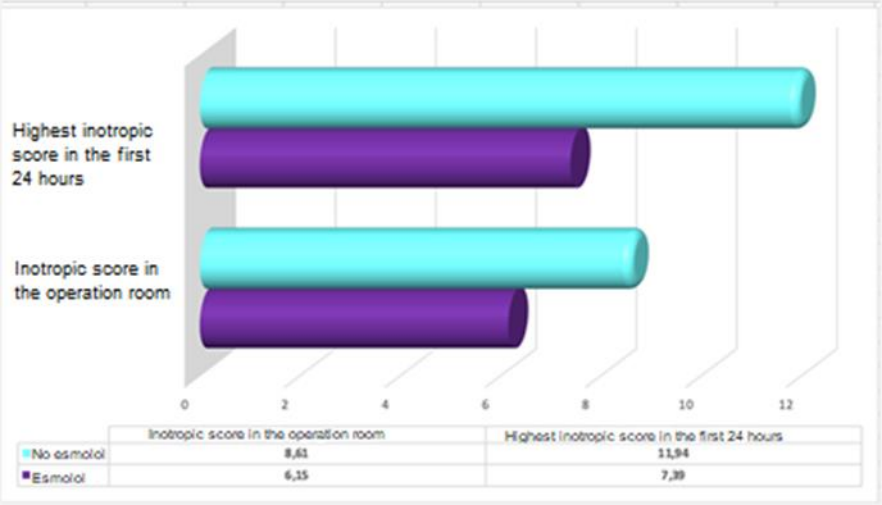

Fig. 2. Inotropic score (IS) in the operating room and its highest value in the first 24 hours in patients divided into those with and without given esmolol

Inotropic support in ICU with statistical significance and vasopressor support with borderline significance were in a lower percentage applied after 24 hours (p=0.001, p=0.066; respectively) (Table 3, Figure 3).

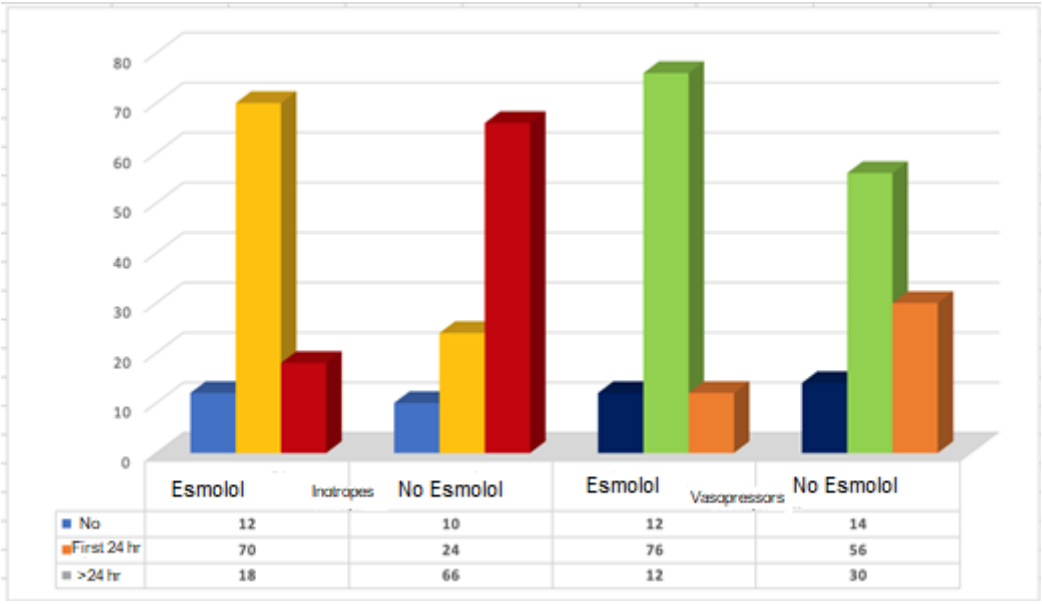

Fig. 3. Percentage representation/non-representation of inotropes and vasopressors in ICU in the first 24 hours and after 24 hours in patients divided into those with and without given esmolol

In the first 24 hours, the highest dose of epinephrine was 0.02±0.01 mcg/kg/min in patients receiving esmolol compared to 0.03±0.02 mcg/kg/min in the control group (p=0.001),

and, the highest dose of norepinephrine was 0.095±0.27 mcg/kg/min in the esmolol group compared to 0.088±0.07 in the control group (p=0.025) (Table 3).

The serum lactate level in the first 3 hours was 2.29±1.15 mmol/L in patients receiving esmolol compared to 3.41±3.69 mmol/L in the control group of patients (p=0.020) (Table 3, Figure 4).

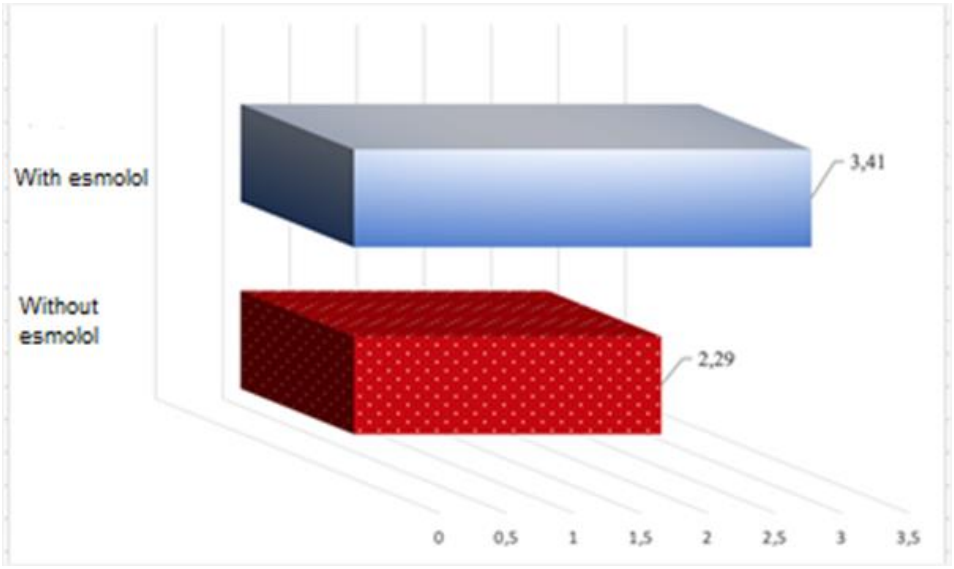

Fig. 4. Serum lactate level in the first 3 hours in patients divided into those with and without given esmolol

Discussion

Coronary artery bypass surgery (CABG) as a myocardial revascularization technique is associated with numerous complications as a result of perioperative myocardial ischemia despite the use of numerous cardioplegic solutions that are the gold standard in cardiac surgery for myocardial protection during cardiopulmonary bypass[1-7].

Our study included 100 patients aged 40-80 years with coronary artery disease that, according to the recommendations of professional associations[29], refers to revascularization with CABG. Patients were randomized into two groups according to whether they received esmolol-beta1-selective adrenergic blocker or placebo.

Patients in both groups were almost identical in age, averaging about 65 years, with a slightly higher female representation (30%) in the esmolol group compared to that (16%) in the control group of patients.

Regarding clinical classifications (NYHA and CCS class), as well as surgical scores (EuroSCORE and STS score), patients in the esmolol group had insignificantly lower values, that is, more favorable clinical and pre-surgical performance.

Regarding risk factors for atherosclerosis, there was no statistically significant difference in their representation in patients with and without given esmolol.

In our study, a comparison was made of the need for inotropic and vasopressor perioperative and postoperative support in both groups of patients, that is, the value of the inotropic score in the operating room and in the first 24 hours was compared. In doing so, we identified that the inotropic score in the operating room was statistically insignificant (p=0.141),

and the highest inotropic score in the first 24 hours was statistically significantly lower (p= 0.002) in patients who received esmolol compared to others.

The percentage representation of inotropes at the exit from the operating room was almost identically distributed in both groups of patients.

Inotropic support in ICU with statistical significance (p=0.0001) and vasopressor support with borderline significance (p=0.06) were applied in a lower percentage after 24 hours in patients given esmolol.

The highest dose of epinephrine in the first 24 hours was statistically significantly lower (p=0.001), that is, the highest dose of norepinephrine was statistically significantly lower in patients receiving esmolol compared to others (p=0.025).

Lactate level in the first 3 hours was statistically significantly lower (p=0.020) in patients in the esmolol group compared to others.

The etiology of perioperative myocardial necrosis and postischemic myocardial dysfunction after cardiac surgery is multifactorial. Myocardial ischemia and necrosis may occur as a result of anesthetic factors, atrial cannulation, myocardial distension, plaque rupture or platelet embolism, and graft spasm or thrombosis. Despite the significant progress achieved in the last 20 years, patients at high risk of heart surgery, including those with unstable angina, poorer ventricular function, diabetes and advanced age continue to manifest postoperative complications such as low cardiac output, perioperative myocardial infarction and heart failure requiring prolonged intensive care. In most cases, the complications are due to ischemic-reperfusion injury and inadequate protection of the myocardium.

Ischemic-reperfusion injury manifests as postischemic stunning, which is reversible, and apoptosis and/or necrosis, which are irreversible. Myocardial stunning is an injury that lasts hours to days despite restoration of normal blood flow. Typically, these patients require some type of temporary support such as inotropes and vasopressors in the immediate postoperative period in order to maintain an adequate cardiac output. Stunned cardiomyocytes show minimal ultrastructural damage that resolves within hours to days after recovery from ischemia. Apoptosis, or programmed cell death, on the other hand, is a pattern of cell death that affects single cells. Prolonged ischemia results in necrotic cell death. Dying cells may show features of both apoptosis and necrosis, that is, nuclear condensation and/or plasma membrane damage[5,6,8].

Myocardial protection in the operating room refers to strategies and methods used to reduce or prevent perioperative infarction and/or postischemic ventricular dysfunction. Administration of BBs belongs to pharmacological cardioprotective methods to protect the myocardium, which includes use of a cardioprotective agent before aortic clamping, adding a pharmacological agent to the cardioplegic solution, or administration of a cardioprotective agent at the time of removal of the aortic clamp or a combination of all these different approaches[5-12]. Most BBs given in the perioperative period reduce myocardial injury during ischemia and reperfusion, but since most of them have a prolonged (hours) negative inotropic and chronotropic effect, their use during cardiac surgery is limited[13-15].

Esmolol is an ultra-short-acting BB that represents a cardioselective BB, with a half-life of about 9 minutes due to esterase hydrolysis, which allows its negative inotropic effect to be quickly terminated after the infusion is reduced or stopped[16-17].

Esmolol reduces myocardial metabolic demands before and during cardioplegic arrest, reducing ischemia-reperfusion injury. If given before aortic clamping, esmolol reaches the coronary microcirculation and provides cardiac protection before the administration of cardioplegia itself[18]. In addition, if added to the cardioplegic solution, esmolol may provide

additional protection by reducing myocardial activity[19-21]. Over the years, meta-analyses of randomized trials[23,30-34] have been performed, which have confirmed that if esmolol is administered during a cardiac surgery, the rate of perioperative myocardial ischemia, occurrence of arrhythmias after CABG, as well as a reduced need for inotropic support in the postoperative period is reduced.

Because of these properties, esmolol is the drug of first choice for use as an adjuvant to cardioplegia in patients in whom there might appear possible side effects (hypotension, bradycardia, heart failure)[22-28] of the given longer-acting BBs administered in the intraoperative period.

Conclusion

A pharmacological cardioprotective method to protect the myocardium with a beta-1 selective adrenergic blocker - esmolol given as an adjunct before and during cardioplegia in patients with coronary artery disease has a positive effect in reducing the inotropic score, respectively less use of inotropic and vasopressor support in the perioperative and postoperative period after coronary artery bypass surgery.

Conflict of interest statement. None declared.

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