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Esmolol cardioplegia in unstable coronary revascularisation patients

A randomised clinical trial

T. RINNE[1], A. HARMOINEN[2] and S. KAUKINEN[1]
[1]*Department of Anaesthesia and Intensive Care, and* [2]*Department of Clinical Chemistry, Tampere University Hospital, and Medical School, University of Tampere, Finland*

Background: Esmolol has been studied and applied to control hypertension and tachycardia during open heart surgery. Esmolol has been used on a minor scale as a single cardioplegic agent. Little information is available on esmolol as a component of blood cardioplegia. In this prospective, randomised, double-blind clinical study we investigated whether esmolol improves cardioprotection in patients scheduled for an urgent coronary operation.
Methods: Forty patients with unstable angina were operated using cold blood cardioplegia as the basic cardioprotective method. Cardioplegia was infused intermittently, and esmolol was given into the cardioplegia line (15 mg/min) during cold infusions. Patients with ongoing myocardial infarction were excluded.
Results: The arrest time during the cardioplegic induction or the rate of spontaneous resumption of the heart rhythm did not differ significantly between the groups. The serial measurements of plasma creatine kinase MB-fraction activity (P=0.27), serum creatine kinase MB-fraction mass assay (P=0.16), troponin I (P=0.41) and myoglobin (P=0.14) similarly did not differ between the groups, nor did myocardial lactate extraction (P=0.12).
Conclusion: Esmolol addition to blood cardioplegia did not increase the efficacy of cardioprotection in the present study setting in unstable patients during urgent coronary revascularisation.

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Key words: Coronary artery bypass; cardioplegic solutions: blood cardioplegia; adrenergic beta-antagonists: esmolol; contractile proteins: troponin I; randomized clinical trial.

ESMOLOL is a cardioselective beta-blocker with an elimination half-life of 9 min (1). Its effects on haemodynamics and metabolism have been investigated during coronary bypass operations (2, 3), and it has also been used as the sole cardioprotective agent (4). Sweeney and Frazier introduced an alternative approach for managing the heart without aortic cross-clamping or cardiopulmonary bypass using esmolol infusion and circulatory assistance (5–8). Little information is available about esmolol in association with blood cardioplegia. When esmolol-enriched crystalloid cardioplegia was compared with a modified St. Thomas's plegia solution during coronary revascularisation, the former resulted in quicker asystole and less frequent dysrhythmias and ST-segment depressions after cross-clamp release (9).

This study was designed to investigate the effects of esmolol on cardioprotection with blood cardioplegia. We hypothesised that esmolol addition to cardioplegia might produce more rapid cardiac arrest, and thereby enhance myocardial perfusion and cardioprotection. Patients with unstable myocardial ischaemia scheduled for urgent primary coronary revascularisation were enrolled. The study protocol included recording of the arrest time and the mode to resume heart beat. Myocardial protection was assessed with cardiac troponin I (cTnI), a regulatory protein specific to myocardium and a highly specific and sensitive marker of perioperative myocardial injury and infarction (10–12). cTnI detects patients with residual ischaemia after cardiac operations very early (13), and has been suggested as a reliable method for comparing various techniques of cardioprotection (14–16). The other parameters were creatine kinase MB-fraction activity (CK-MB) and mass assay (CK-MBm), myoglobin concentration, myocardial lactate balance, and routine 12-lead electrocardiogram (ECG).

Methods

The study plan was approved by the Ethics Committee of Tampere University Hospital and the National

Agency for Medicines. Forty patients admitted for acute myocardial ischaemia gave their written informed consent to the prospective, randomised, double-blind, placebo-controlled study. All were to be operated urgently for primary coronary revascularisation, with cold blood cardioplegia used as the routine cardioprotective method. The operations took place either after a successful medical stabilisation period, or in unstable pain with maximal medical treatment during the same hospitalisation. The exclusion criteria were an acute myocardial infarction, severe cardiac failure or bradycardia, advanced renal or hepatic dysfunction, or history of adverse effects provoked by beta-blocking agents.

All patients received oral lorazepam and intramuscular scopolamine/morphine premedication plus the daily medication, including beta-blockers, on the operation day. Late use of acetosalicylic acid, low molecular weight heparin, or nitroglycerine infusion was recorded. Anaesthesia and cardiopulmonary bypass (CPB) were provided by one anaesthesiologist (TR), blinded to the study group.

A radial artery line and pulmonary artery catheter were inserted for haemodynamic monitoring. Cardiac output measurements by the thermodilution method were obtained before the induction of anaesthesia, after admission to the intensive care unit (ICU), and on the following morning. Anaesthesia was induced with sufentanil (0.8 μg/kg, continued with 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$), midazolam (0.1 mg/kg, continued with 1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and pancuronium (0.1 mg/kg). The infusions were adjusted according to clinical demands, with isoflurane given as necessary. Total doses of sufentanil and midazolam were recorded before transferring the patients to the ICU, where the infusions were adjusted to maintain analgesia and sedation.

CPB was instituted with regular cannulation technique using mild hypothermia (32°C). Aprotinin priming of the perfusion circuit (2 000 000 IU), or tranexamic acid (1.5–2 g), were given to control bleeding. Postoperative autotransfusion of the mediastinal blood was used in the ICU. A retrograde coronary sinus cannula was inserted transatrially for cardioplegia infusions and lactate samples. The first cardioplegia infusion was given for 1.5 min antegradely, or until the cardiac asystole was reached, and then retrogradely for 2–3 min. Subsequent cardioplegia infusions were given after the completion of each distal anastomosis. The proximal anastomoses were constructed mainly by partial clamping of the aorta, while normal blood was supplied through the vein grafts. Occasionally the single-clamp technique was used at the surgeon's discretion.

The 20 patients in the esmolol group received esmolol (Brevibloc®, 10 mg/ml, Leiras Oy, Finland) at a dose of 15 mg/min into the cardioplegia line by manual control during the cold cardioplegia infusions, producing a calculated average concentration of 50–60 μg/ml. The 20 control patients received an equal volume of normal saline. The final warm cardioplegia before aortic unclamping (AU) was infused without esmolol, as in this study we emphasised the induction stage of cardioplegia infusion.

Baseline samples of plasma CK-MB activity, serum CK-MB mass, cTnI and myoglobin concentrations were taken after the anaesthesia induction. CK-MB activity was then measured on the operation day (6 p.m.) and on the 1st and 2nd postoperative morning, and cTnI, CK-MBm and myoglobin on the 1st and 3rd postoperative day. CK-MB was immediately assayed at 37°C, with the normal range 0–25 U/l. All the other blood samples were stored deep-frozen (−70°C) for later determination. CK-MBm, cTnI and myoglobin were measured with a Chiron ACS 180 Plus analyser (Chiron Diagnostics, Ltd., Halstead, Essex, U.K.) using a direct chemiluminometric method. The detection limit for cTnI was ≤0.15 μg/l, and the diagnostic cut-off for myocardial infarction (MI) set at 1.5 μg/l. The corresponding detection limits for myoglobin and CK-MBm were 3 μg/l and 0.18 μg/l, with values above 110 μg/l and 5.0 μg/l, respectively, suggestive of MI.

Simultaneous arterial and coronary sinus whole blood samples for lactate analysis were taken after insertion of the retroplegia cannula and after 5 min of reperfusion. The myocardial lactate extraction [(arterial lactate−coronary sinus lactate)/arterial lactate×100] and the net change in the extraction rate between the two time points was calculated.

Data were analysed using SPSS software. The Chi-square or Fisher's exact test were used for categorical variables, and Mann-Whitney U-test for data on the ordinal scale. Continuous variables were analysed by Student's t test or analysis of variance for repeated measures. Logarithmic transformation was done when the variables were not distributed normally. The baseline values were taken as co-variates for repeated measures. Correlations were tested with Pearson's correlation coefficient. Data are expressed as absolute numbers or means (SD), or medians with the interquartile range when appropriate. Statistical significance was determined at the level of $P<0.05$.

Results

The preoperative and operative characteristics are presented in Table 1, and the study parameters related

Table 1

Patient characteristics and operative details.

	Control n=20	Esmolol n=19
Age (yr)	63.6 (10.6)	64.4 (8.6)
Height (cm)	165 (7)	170 (10)
Weight (kg)	78.5 (14.0)	85.8 (11.2)
Body surface area (m^2)	1.95 (0.19)	2.05 (0.17)
Female/Male (n)	7/13	7/12
Hypertension (n)	10	10
NYHA (2/3/4) (n)	0/7/13	1/4/14
Previous MI (n) 0/1/2 /patient (n)	9/9/2	11/7/1
EF (%)	53 (13)	61 (15)
ASA/LMWH continued up till operation	6/7	11/9
Postop. blood discharge, 12 h (ml)	651 (379)	749 (413)
Nitroglycerine infusion up till operation	1	1
Perfusion time (min)	84 (24)	97 (28)
Cross-clamping time (min)	59 (20)	65 (19)
Distal anastomoses (n)	3.5 (1.3)	3.5 (1.0)
IMA-grafts (n)	20	19
Single-clamp technique	5	7

Data as mean (SD) or absolute numbers. No statistical differences between the groups. MI: Myocardial infarction; ASA: acetosalicylic acid; LMWH: Low molecular weight heparin; IMA: Internal mammary artery.

Table 2

Study parameters related to cardioplegic induction and clamp release.

	Control n=20	Esmolol n=19
Time to asystole (s)	63 (32)	59 (22)
Blood pressure decrease (mmHg)	6 (10)	4 (6)
All DC shocks (n) 0/1–2/3<patient	7/9/4	13/4/2
Spontaneous rhythm (n)	9	14
Pacemaker needed (n)	0	1

Data as mean (SD) or absolute numbers. No statistical differences between the groups. DC: direct current.

to cardioplegic induction and removal of the cross-clamping in Table 2. These parameters did not differ significantly between the study groups, nor did the total volumes of anaesthetic agents, the cardiac index, inotropic support, or postoperative drain discharge. Intraoperative autologic blood donation and aprotinin priming of the perfusion set were similar in both groups. One patient in each group had a re-exploration for mediastinal bleeding. Circulatory assisting devices were only used for one patient in the esmolol group.

Creatine kinase, troponin and myoglobin analyses

The patients with a recent MI were excluded preoperatively from the study following clinical evaluation of their ECG-records and CK-MB activity measurement. Thereby, only one patient in the esmolol group had an elevated cTnI concentration before operation (1.92 μg/l; later on 17.05 and 9.38 μg/l), and was excluded from the study. An abnormal CK/CK-MB ratio was seen in one patient in the control group, suggesting an extracardiac source, and these results were excluded from the comparisons. Table 3 presents the median and interquartile values of CK-MB activity ($P=0.27$), CK-MBm ($P=0.16$) and myoglobin ($P=0.14$). Fig. 1 depicts the cTnI values ($P=0.41$). The net reduction in lactate extraction over the sampling interval did not differ between the groups ($P=0.12$, Fig. 2).

The correlations between cTnI and the corresponding CK-MBm values varied from moderate to weak (R=0.848 at the first postoperative time point and R=0.609 at the second). The correlation between both postoperative measurements for cTnI was also moderate (R=0.859) but no correlation existed between the CK-MBm measurements (R=0.220). The strongest correlation was observed between the first postoperative values of cTnI and the second of CK-MBm (R=0.892). The myoglobin values did not correlate with the other markers.

Electrocardiograph and myocardial infarction

Two patients in both groups had a new Q-wave in the ECG the following morning. They had very high immediate postoperative cTnI peak values (100.5, 89.5, 88.4 and 49.5 μg/l). After excluding these patients, cut-off values for CK-MB activity and mass, and TnI were defined as mean+2SD (92 IU/l, 63 μg/l, and 28 μg/l respectively). MI was detected when all three markers exceeded the cut-off limits. These criteria found five patients with acute MI, three in the control group and two in the esmolol group.

One patient in the esmolol group had to be paced for a short time after removal of the cross-clamp. Atrioventricular conduction times and the incidence of conduction disturbances did not differ between the groups.

Complications

One patient in the esmolol group died on the operation day. All the cardiac markers were normal before operation. The procedure was complicated by an insufficient flow in the internal mammary artery graft, which had to be re-constructed as a free graft into the aorta. The patient had a severe low output syndrome in the ICU, and counterpulsation therapy was attempted. However, this failed due to sclerotic inguinal vessels. The highest postoperative CK-MB value was detected, and a new Q-wave in the ECG. Autopsy revealed a perioperative infarction.

Table 3

Serum CK-MB activity, CK-MB mass and myoglobin values.

	CK-MB IU/l				CK-MBm μg/l			Myoglobin μg/l		
	Preop	Opday	Postop1	Postop2	Preop	Postop1	Postop3	Preop	Postop1	Postop3
Control	7 (4)	39 (28)	42 (39)	18 (18)	0.6 (0.9)	16.1 (31.5)	2.2 (2.0)	39 (19)	469 (480)	105 (104)
Esmolol	8 (4)	44 (22)	39 (50)	25 (21)	0.9 (0.7)	14.4 (44.9)	3.1 (4.9)	38 (22)	532 (596)	164 (235)
			P=0.27			*P*=0.16			*P*=0.14	

Data as median (interquartile range). Analysis of variance for repeated measures: *P*-value between the groups. CK-MB: creatine kinase MB isoenzyme activity; CK-MBm: creatine kinase MB isoenzyme mass concentration; Preop: before operation; Opday: operation day; Postop1, 2, 3: first, second and third postoperative days.

Discussion

In the present study esmolol was combined with conventional cold blood cardioplegia, and the main objective was to improve cardioprotection during coronary revascularisation in patients with unstable myocardial ischaemia. We assumed that the differences might be more obvious in unstable patients, since catecholamine stimulation would increase the requirements for cardioprotection. However, we were unable to demonstrate any improved cardioprotection with esmolol supplementation. All the biochemical markers had consistently slightly lower values in the control group, though the differences were not statistically significant.

We expected to notice more rapid arrest in patients receiving esmolol but the difference was not statistically significant. However, the most immediate parameters, such as the number of applied direct current shocks, spontaneous resumption of the cardiac rhythm, and the lactate extraction were slightly enhanced in the esmolol group but again without statistical significance.

Cork et al. have discussed the mechanisms through which beta-adrenergic antagonists might provide cardioprotection during CPB (3). These include the basic reduction of oxygen and adenosine triphosphate consumption (17, 18), decreased lipase activity (19), increased blood flow to ischaemic regions (20), and reduced calcium influx and reperfusion injury by fatty acids (21, 22). Beta-blockers may also prevent atherosclerotic plaque rupture and consequent coronary thrombosis (23). Esmolol has reduced oxygen free radical formation and arachidonic acid metabolism during early reperfusion in an experimental canine model (24).

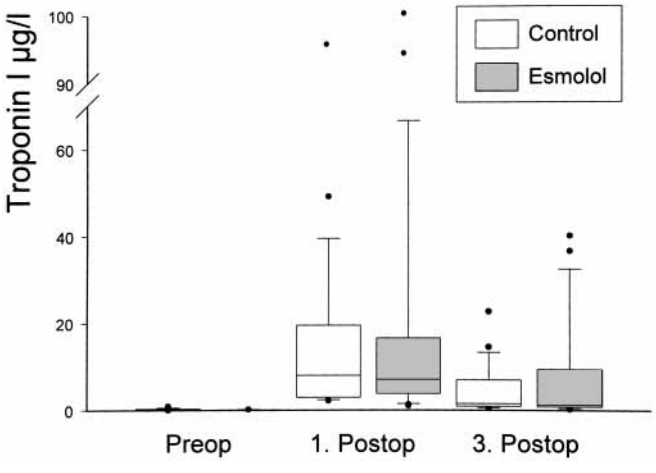

Fig. 1. Serum troponin I concentrations of both groups: the median, 10th, 25th, 75th and 90th percentiles with outliers, (P=0.41). Preop: Preoperative, 1. Postop: 1st postoperative day, 3. Postop: 3rd postoperative day.

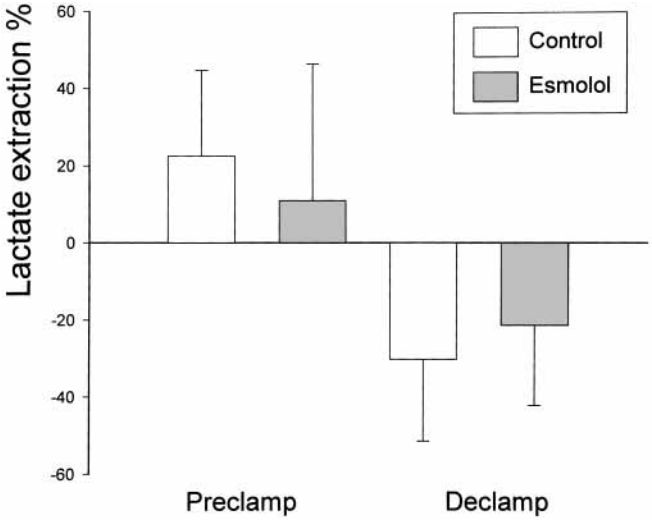

Fig. 2. Lactate extraction of both groups at the two sampling points: mean (SD), (P=0.12). Preclamp: Before aortic clamping, Declamp: 5 min after aortic unclamping.

In the present study a low-dose esmolol scheme was used. Esmolol has a metabolite with weak beta-blocking activity (25). It is not known whether this metabolite has a clinically significant cardiac depressant effect after prolonged esmolol infusion. On the other hand, in higher doses, esmolol may have extracardiac properties such as decreased systemic lactate production during CPB, though this may also have resulted from enhanced clearance by increased liver blood flow (3).

Esmolol has previously been used succesfully as a cardioprotective agent (5–8). However, in these studies, no conventional cardioplegia had been used at all. The heart had been maintained in a slowly beating state, supported with circulatory assisting devices or CPB. Improved myocardial lymph flow and reduced oedema have been suggested as important factors enhancing cardiac performance (7). After all, these methods have to be considered as a different type of cardioprotection and an alternative to conventional cardioplegia.

The definition of perioperative myocardial infarction (PMI) may be indefinite by any single parameter. In recent studies, measurement of cTnI has been suggested as a good indicator of perioperative myocardial damage. The cut-off values defined for this purpose have varied markedly, depending on the analysis system, sampling time and patient population, and cannot be compared directly with the results obtained in other institutions. The release of cTnI may also depend on the form of cardioplegia delivery and patency of the native coronary vessels (15, 26).

In the present study, the relatively small number of patients may have limited the validity of the cut-off values. Also, the first postoperative sampling may have missed minor peak values of cTnI release occurring very early after AU. According to Mair et al., patients with PMI have their cTnI peaks occurring later, at about 24 h compared with 8 h in non-PMI patients, after AU (11). Therefore, we most probably detected the major changes in the cardiac markers. However, Birdi et al. have suggested that early sampling is required for comparisons of myocardial protection techniques, but also that sampling for 48 h is necessary for estimating cumulative marker release (16). More delayed sampling may also have clinical importance: one patient in the esmolol group had increasing cTnI and CK-MBm values at the last sampling point (34.65–36.80 and 39.4–67.7 μg/l respectively). However, in situation like this, the factors involved may be other than intraoperative cardioprotection.

In conclusion, the intermittent esmolol supplementation of cold blood cardioplegia, as used in the present study setting, did not result in more rapid arrest or enhanced cardioprotection during urgent coronary revascularisation in unstable patients. No prolonged sinus arrest or other adverse effects that could be attributed to beta-blockade were noticed. Inclusion of esmolol in the final warm cardioplegia infusion might have been advantageous but this remains to be established in further studies.

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Address:
Dr. *Timo Rinne*
Department of Anaesthesia and Intensive Care
Tampere University Hospital
PO Box 2000
FIN-33521 Tampere
Finland
e-mail: timo.rinne@pp.fimnet.fi