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Original Article

# Esmolol in Cardiac Surgery: A Randomized Controlled Trial

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*Objective:* To assess whether the administration of the ultra-short–acting β-blocker esmolol in cardiac surgery could have a cardioprotective effect that translates into improved postoperative outcomes.

*Design:* Single-center, double-blinded, parallel-group randomized controlled trial.

*Setting:* A tertiary care referral center.

*Participants:* Patients undergoing elective cardiac surgery with preoperative evidence of left ventricular end-diastolic diameter >60 mm and/or left ventricular ejection fraction <50%.

*Interventions:* Patients were assigned randomly to receive either esmolol (1 mg/kg as a bolus before aortic cross-clamping and 2 mg/kg mixed in the cardioplegia solution) or placebo in a 1:1 allocation ratio.

*Measurements and Main Results:* The primary composite endpoint of prolonged intensive care unit stay and/or in-hospital mortality occurred in 36/98 patients (36%) in the placebo group versus 27/102 patients (27%) in the esmolol group (p = 0.13). In the esmolol group, a reduction in the maximum inotropic score during the first 24 postoperative hours was observed (10 [interquartile range 5-15] *v* 7 [interquartile range 5-10.5]; p = 0.04), as well as a trend toward a reduction in postoperative low-cardiac-output syndrome (13/98 *v* 6/102; p = 0.08) and the rate of hospital admission at one year (26/95 *v* 16/96; p = 0.08). A trend toward an increase in the number of patients with ejection fraction ≥60% at hospital discharge also was observed (4/95 *v* 11/92; p = 0.06).

*Conclusions:* In the present trial, esmolol as a cardioplegia adjuvant enhanced postoperative cardiac performance but did not reduce a composite endpoint of prolonged intensive care unit stay and/or mortality.



*Key Words:* esmolol; cardiac surgery; cardiopulmonary bypass; β-blockers

CARDIOPULMONARY bypass (CPB) is key to success in cardiac surgery, sustaining organ perfusion while providing a bloodless field.[1] To temporarily paralyze the heart and allow myocardial protection from ischemia during aortic cross-

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clamping, cardioplegia is administered into the coronary arteries. Protection of the myocardium is paramount because mitigating the effects of ischemia is crucial for weaning from CPB and reducing in-hospital mortality. Even though organ protection research has achieved great advances over the last decade, in-hospital mortality after cardiac surgery still lies around 3%, mostly because of the development of postoperative cardiac failure.[2] In light of this, any possible strategy able to improve the protection of the heart during the ischemic arrest may help to minimize postoperative complications and improve the outcome.

The perioperative role of β-blockers has been a hot topic in both cardiac and noncardiac surgery in recent years because of their favorable pharmacologic profile. However, despite the well-known effects on the decrease of myocardial oxygen consumption and of the sympathetic response to the surgical stimuli, which make these drugs ideal to use in the perioperative period in patients at risk of cardiac events, the results of large randomized clinical trials (RCTs) are mixed.[3–5] In fact, if on the one hand the administration of long- lasting β-blockers reduces the rate of perioperative cardiovascular complications, on the other hand, a prolonged hypotension may lead to major neurologic events.[6] Current guidelines advise to consider switching patients on chronic β-blockers therapy to short-acting agents to limit adverse events.[7] Thus, esmolol, an ultrashort–acting β-blocker highly selective for $\beta_1$ receptors, may combine the beneficial effects of β-blockers on cardiac metabolism without the detrimental effects of long-acting agents.[8] With a nine-minute half-life and an esterase-based metabolism, esmolol might play a crucial role in decreasing myocardial metabolic demands both before and during cardioplegic arrest. Esmolol can be administered to reduce myocardial oxygen consumption, either a few minutes before aortic cross-clamping[9] while the heart is still beating, or it can be added to cardioplegic solutions to enhance heart protection from ischemia.[10]

A few studies investigated the role of esmolol in reducing perioperative ischemia and arrhythmias after cardiac surgery and were summarized in a recent meta-analysis.[11] No study performed long-term follow-up. The aim of the present study was to test the hypothesis that esmolol, given before aortic cross-clamping and with Custodiol cardioplegia, reduces the rate of a composite outcome of prolonged intensive care unit (ICU) stay and mortality as a result of superior myocardial protection and better cardiac contractility after weaning from CPB. A one-year follow-up also was performed in study participants.

## Methods

A double-blinded, parallel-group, single-center RCT was performed. The study protocol was approved by the San Raffaele Hospital Ethical Committee, Milan, Italy, and, therefore, was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The trial protocol was registered at ClinicalTrials.gov (NCT00959569).

All patients undergoing elective cardiac surgery at IRCCS San Raffaele Scientific Institute were screened for eligibility. Patients who were older than 18 years and had preoperative evidence of left ventricular end-diastolic diameter (LVEDD) >60 mm and/or left ventricular ejection fraction (LVEF) <50% were asked for their written informed consent to participate in the study. Patients with a history of previous unusual response to esmolol, esmolol administration in the previous 30 days, or who were undergoing urgent or emergency surgery were excluded from participating in the trial.

Patients were assigned randomly either to the esmolol or the control group in a 1:1 allocation ratio. Patients randomly assigned to the esmolol group received a bolus of 1 mg/kg (up to 100 mg) of esmolol (Brevibloc; Baxter, Deerfield, IL) through the central venous line catheter after aortic cannulation but before aortic cross-clamping. An additional dose of 2 mg/kg (up to 200 mg) was added to standard cardioplegia. The esmolol dose was based on data from the authors' recent meta-analysis[11] and from their previous pilot study.[12] Patients randomly assigned to the control group received saline solution, administered in the same mode and at the same times and volumes as the placebo comparator, which was indistinguishable from esmolol.

The primary endpoint of the study was a composite of prolonged ICU stay (defined as intensive care treatment lasting for three days or longer)[13] or in-hospital mortality. Secondary endpoints were ventricular fibrillation after CPB; low-cardiac-output syndrome (defined as the need for inotropic support or an intra-aortic balloon pump for at least 24 hours consecutively to maintain a cardiac index >2.0 L/min/m$^2$, avoiding metabolic acidosis and urine output <0.5 mL/kg/h)[14]; need for inotropic support; peak cardiac troponin T level within the first two postoperative days; and 30-day mortality.

Details on intraoperative monitoring are described in Table 1. All preoperative medications were discontinued on the day of surgery. Patients received premedication with intramuscular morphine, 0.1 mg/kg, and atropine, 0.5 mg, one hour before surgery. General anesthesia was induced with an intravenous bolus of propofol, fentanyl, and rocuronium and was maintained with fentanyl boluses, continuous infusion of rocuronium and propofol, and inhaled sevoflurane. An intravenous bolus of 1 g of tranexamic acid was administered at the beginning of surgery, followed by a 400 mg/h infusion. A right internal jugular 7-Fr central venous line and an 8.5-Fr percutaneous pulmonary artery sheath introducer with side port were placed in all patients. Standard intraoperative monitoring included an electrocardiogram, pulse oximetry, capnography, urinary output, invasive blood pressure measurement, bladder temperature, and transesophageal echocardiogram. Advanced hemodynamic monitoring with a pulmonary artery catheter was used in selected patients upon physician discretion.

The hemodynamic management was performed according to a standard protocol.[15] Briefly, epinephrine was the first-line inotropic agent and was used in patients with left and/or right ventricular dysfunction at CPB separation upon transesophageal echocardiography monitoring intraoperatively and,

Table 1
Baseline Characteristics of Studied Population

| | Placebo Group (n = 98) | Esmolol Group (n = 102) |
|---|---|---|
| Male patients, n (%) | 68 (69%) | 77 (75%) |
| Age, y (mean ± SD) | 64 ± 11.3 | 61 ± 12.8 |
| Weight, kg (mean ± SD) | 77 ± 12.5 | 77 ± 16.9 |
| Height, cm (mean ± SD) | 169 ± 14.1 | 172 ± 14.7 |
| Medical history | | |
| Previous cardiac surgery, n (%) | 16 (16%) | 14 (14%) |
| Hypertension, n (%) | 61 (62%) | 58 (57%) |
| History of heart failure, n (%) | 24 (25%) | 26 (26%) |
| NYHA class III or IV, n (%) | 12 (12%) | 13 (13%) |
| COPD, n (%) | 11 (11%) | 7 (7%) |
| Atrial fibrillation, n (%) | 20 (20%) | 23 (23%) |
| CAD, n (%) | 24 (25%) | 26 (26%) |
| Diabetes, n (%) | 9 (9%) | 5 (5%) |
| History of stroke or TIA, n (%) | 8 (8%) | 9 (9%) |
| Baseline creatinine, mg/dL (mean ± SD) | 1.0 ± 0.23 | 1.0 ± 0.27 |
| Baseline hematocrit, % (mean ± SD) | 42 ± 5.0 | 41 ± 5.2 |
| ACEF score, mean ± SD | 1.3 ± 0.46 | 1.3 ± 0.49 |
| Preoperative medical therapy | | |
| β-blockers, n (%) | 53 (54%) | 57 (56%) |
| ACE inhibitors, n (%) | 39 (40%) | 37 (35%) |
| Angiotensin receptor blockers, n (%) | 15 (15%) | 19 (19%) |
| Antiplatelet drugs, n (%) | 36 (37%) | 38 (38%) |
| Statins, n (%) | 20 (20%) | 19 (19%) |
| Anticoagulants, n (%) | 10 (10%) | 8 (8%) |
| Diuretics, n (%) | 52 (53%) | 51 (50%) |
| Digoxin, n (%) | 13 (13%) | 12 (12%) |
| Calcium-antagonists, n (%) | 15 (15%) | 11 (11%) |
| Antiarrhythmic drugs, n (%) | 12 (12%) | 9 (9%) |
| Echocardiographic parameters | | |
| Ejection fraction (%, median [IQR]) | 52 [45-59] | 53 [44-60] |
| End diastolic diameter (mm, median [IQR]) | 63 [58-67] | 63 [57-68] |
| Mitral regurgitation, n (%) | 64 (65%) | 57 (56%) |
| Aortic stenosis or regurgitation, n (%) | 45 (46%) | 41 (40%) |
| Interventricular septum >12 mm, n (%) | 16 (16%) | 18 (18%) |
| Intraoperative data | | |
| Duration of CPB (min, median [IQR] | 90 [68-120] | 91 [67-120] |
| Aortic cross-clamping, n (%) | 97 (100%) | 102 (100%) |
| Aortic cross-clamping time (min, median [IQR]) | 66 [50-90] | 68 [49-85] |
| Additional procedures, n (%) | 30 (31%) | 36 (35%) |
| Intraoperative transfusion, n (%) | 14 (14%) | 11 (11%) |
| Pacemaker post CPB, n (%) | 57 (58%) | 68 (67%) |
| Minimum hematocrit during CPB, % (mean ± SD) | 27 ± 4.7 | 26 ± 3.6 |
| Type of surgery | | |
| Mitral valve surgery, n (%) | 61 (62%) | 65 (64%) |
| Aortic valve surgery, n (%) | 39 (40%) | 42 (41%) |
| CABG, n (%) | 10 (10%) | 18 (18%) |
| Combined surgery, n (%) | 43 (44%) | 43 (42%) |

Abbreviations; ACE, angiotensin-converting enzyme; ACEF, age creatinine ejection fraction score; CABG, coronary artery bypass grafting; CAD coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation; TIA, transient ischemic attack.

mainly, transthoracic echocardiography monitoring after ICU admission.

Norepinephrine was the first-line vasoconstrictor and was used in patients with vasoplegia, defined as a normal or supranormal cardiac output along with low systemic vascular resistance.

The decision to place an intra-aortic balloon pump was based on a team decision among the attending anesthesiologist, cardiac surgeon, and cardiologist. As is the authors' standard practice, intra-aortic balloon pump insertion was evaluated when the vasoactive inotropic score approached 20, but a comprehensive evaluation involving circulatory status and echocardiography plays a key role in the final decision.

A temperature of 32-to-34°C and a target mean arterial pressure of 65 mmHg were maintained during CPB. Unfractionated heparin (at a starting dose of 3 mg/kg) was administered to maintain an activated clotting time of more than 480 seconds during CPB. Cold Custodiol histidine-tryptophan-ketoglutarate (HTK) cardioplegic solution (Dr. Franz-Köhler Chemie GmbH, Bensheim, Germany) was administered to achieve myocardial protection during aortic cross-clamping. Upon aortic cross-clamping, a total dose of 1 mL/1g of myocardial tissue of Custodiol HTK solution at 4°C was used to stop the heart. Myocardial weight was estimated as 0.5% of total body weight in adult patients. Antegrade administration in the aortic root was the preferred method of cardioplegia administration. If selective cardioplegia administration was required by the attending cardiac surgeon, 70% of the total dose was administered in the left main coronary artery and 30% was administered in the right coronary artery. If retrograde cardioplegia administration also was deemed necessary, 40% of the total dose was administered in the coronary sinus. Cardioplegia was repeated if cardiac ischemia time was more than 120 minutes (40% of initial dose) or if any signs of electromechanical cardiac activity became evident before the surgeons were ready to remove the aortic clamp. Protamine was used to revert administered heparin in a 1:1 ratio at the end of CPB.

After surgery, patients were transferred to the ICU. Weaning from mechanical ventilation was started if hemodynamics were stable and no apparent bleeding was ongoing as soon as an adequate level of consciousness and normothermia were obtained. Standard therapy also included hydration, ranitidine, morphine for pain relief, antibiotic prophylaxis with cefazoline, diuretics, and inotropic drugs and mechanical circulatory support devices when deemed necessary by the attending physician.

Postoperative β-blockers administration was restarted as soon as hemodynamic conditions allowed. All other drugs were reevaluated before they were restarted. No other specific drug was given routinely for cardiac protection.

Four blood samples to dose troponin T were drawn at the following fixed time points: upon ICU arrival, four hours after the end of surgery, and on the first and second postoperative days. The highest value among these for each patient was recorded as peak postoperative troponin.

A computer-generated list of random numbers was used for the allocation of study participants. Participants were assigned a progressive randomization number. The corresponding sealed, progressively numbered, opaque envelope containing information about patient allocation was opened by an independent trained researcher.

The study drug (esmolol or placebo) was prepared according to protocol procedures. Then, the preparation was given to the blinded attending anesthesiologist. All the physicians, patients, and data analysts were kept blinded to the allocation. Outcome and safety data were collected daily at the bedside from the patients' charts by another blinded independent researcher until hospital discharge, and these were stored in the appropriate case report form. A telephonic 30-day follow-up was performed to assess survival. No additional intervention or laboratory examinations were performed specifically for the trial.

The vasoactive inotropic score was calculated using the following formula:

$$\text{Dobutamine dose } [\mu g/kg/\text{min}] + \text{Dopamine dose } [\mu g/kg/\text{min}] + \text{Enoximone dose } [\mu g/kg/\text{min}] + (\text{Epinephrine dose } [\mu g/kg/\text{min}] \times 100) + (\text{Norepinephrine dose } [\mu g/kg/\text{min}] \times 100)$$

High inotropic support in this protocol was defined as a vasoactive inotropic score >10.[16]

Mild hypotension was defined as mean arterial pressure <55 mmHg during CPB. Bradycardia was defined as a decrease in heart rate <60 beats per minute.

Mild pulmonary injury was defined according to the 2012 Berlin definition as lung injury of acute onset, bilateral opacities on chest x-ray not explained by other lung pathology, respiratory failure not explained by heart failure or volume overload, and a ratio of partial pressure arterial oxygen and fraction of inspired oxygen between 201 and 300 mmHg (≤39.9 kPa), with a minimum positive end-expiratory pressure of 5 $cmH_2O$.[17]

Standardized criteria for ICU discharge to the postoperative cardiac surgery ward were used, as follows: peripheral capillary oxygen saturation ≥94% with a fraction of inspired oxygen ≤0.5 by face mask, adequate hemodynamic stability, absence of clinically significant arrhythmias, chest tube drainage <50 mL/h, urine output >0.5 mL/kg/h, no intravenous inotropic or vasopressor therapy, and no seizure activity. Criteria for hospital discharge were hemodynamic and cardiac rhythm stability, presence of clean and dry incisions, absence of fever, normal bowel movement, and independent ambulation and feeding.

Data about hospital stay were recorded on discharge. In the authors' practice, patients are sent to a rehabilitation facility after cardiac surgery early, as soon as all major clinical issues are resolved, including the need for circulatory support and oxygen. There, patients usually undergo an additional 14-day rehabilitation cycle after discharge.

Data were stored electronically and analyzed with Stata 15.1 (StataCorp LP, College Station, TX) software. All data analysis was performed according to a preestablished intention-to-treat analysis plan. Dichotomous data were compared using a two-tailed chi-square test with the Yates correction or Fisher exact test, when appropriate. Continuous measurements (including primary outcome) were compared using the *t* or Mann-Whitney *U* test, as appropriate. Two-sided significance tests were used throughout. Data are presented as medians (interquartile range [IQR]) or as means ± standard deviation, as appropriate.

Sample size calculation was based on a two-sided alpha error of 0.05 and 80% power. On the basis of the authors' experience investigating ICU stay and mortality after cardiac surgery, they anticipated that 60% of patients would reach a composite endpoint of in-hospital death and/or prolonged ICU stay in the control group and 40% of patients in the treatment group. Therefore, they calculated that a sample size of 97 patients per group would be needed in order to take into account possible protocol deviations.

## Results

The study included 200 patients who underwent cardiac surgery at the authors' institution, with recruitment completed in May 2018 and the one-year follow-up completed in May 2019. Ninety-eight patients were assigned randomly to receive placebo, and 102 patients received esmolol. All of the 200 randomly assigned patients received the assigned treatment and were analyzed for the primary outcome. The 30-day and in-hospital follow-up were completed for all patients, and no patient was excluded from the analyses. The randomization flowchart as per the CONSORT 2010 guidelines is shown in Fig. 1.

Patients' baseline characteristics were similar between groups (see Table 1). Patients were 62 ± 12.2 years old, 145/200 patients (73%) were male, and the most common intervention (190/200 [95%]) was valve surgery. Median CPB duration was 90 minutes (68-120).

The mean dose of esmolol administered was 78 ± 15.0 mg before aortic cross-clamping and 155 ± 29.9 mg with the cardioplegic solution.

The primary endpoint of prolonged ICU stay and mortality occurred in 36/98 patients (37%) in the placebo group versus 27/102 (26%) patients in the esmolol group (p = 0.13; risk difference [95% confidence interval {CI}] −0.10 {−0.23 to 0.03}]) (Table 2). A planned subanalysis considering patients with both LVEF ≤50% and LVEDD ≥60 mm confirmed a trend toward a beneficial effect of esmolol on the primary outcome: 10/24 (42%) in the placebo group versus 6/24 (25%) in the treatment group (p = 0.19; risk difference [95% CI −0.17 {−0.43 to 0.10}]) (Supplemental Fig 1). An exploratory subanalysis in patients with LVEF ≤50% and LVEDD ≥70 mm confirmed a trend toward a beneficial effect of esmolol on the primary outcome: 5/8 (63%) *v* 1/8 (13%); p = 0.12) (see Supplemental Fig 1). An additional exploratory subanalysis was performed to understand the role of perioperative β-blockers on the primary outcome; among patients not on preoperative therapy, the primary outcome was reached in 16/45 (36%) of patients in the placebo group versus 9/45 (20%) in the esmolol group (p for interaction = 0.16).

Postoperative low-cardiac-output syndrome was reported in 13/98 (13%) patients in the placebo group and 6/102 (6%)

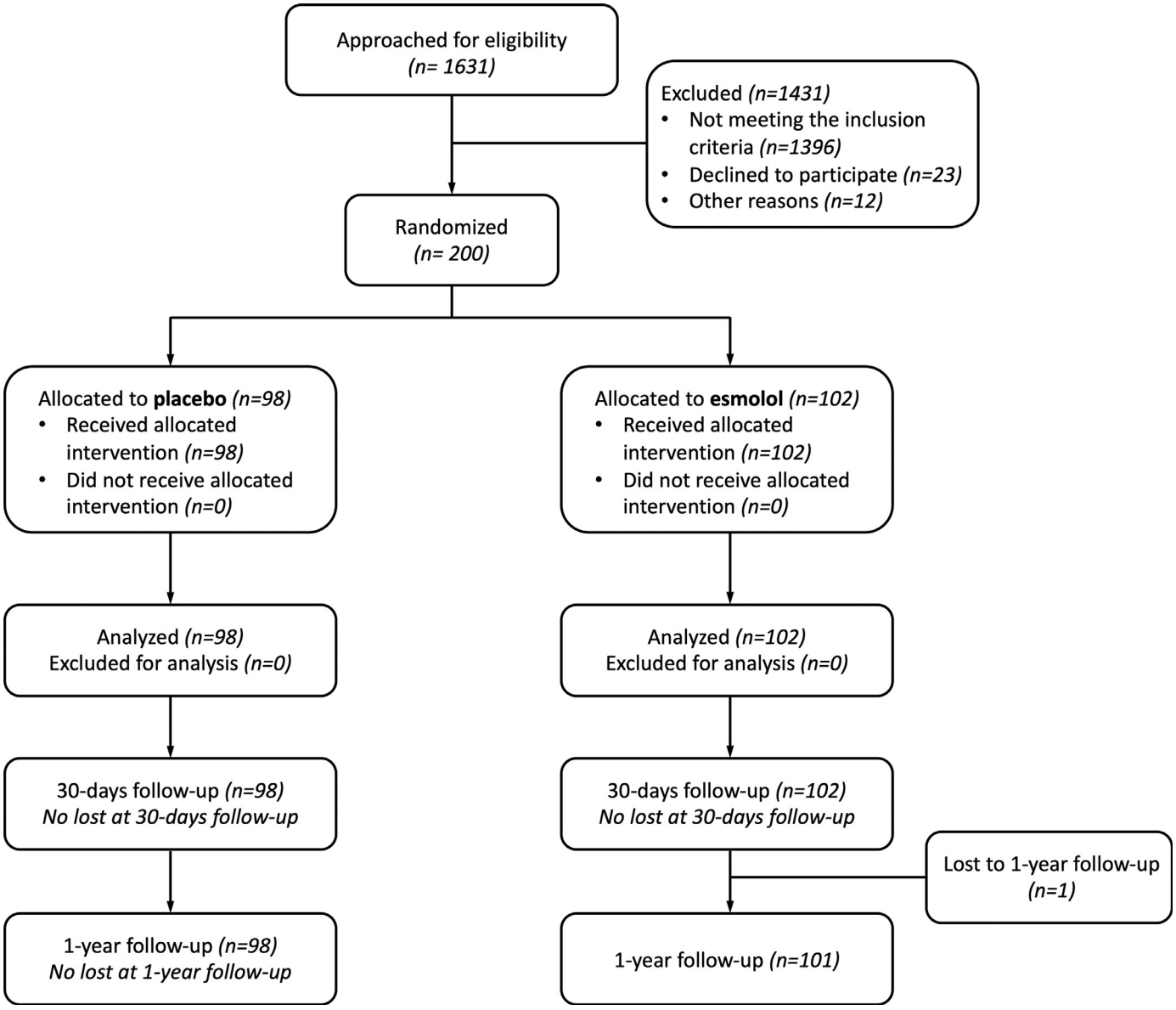


Fig. 1. Study flowchart.

patients in the esmolol group (p = 0.08; risk difference [95% CI −0.03 {−0.13 to 0.8}]). Need for mechanical circulatory support with intra-aortic balloon pump was similar between the two groups (18 [18%] *v* 16 [16%]; p = 0.60).

Three (2.9%) patients in the esmolol group and none in the placebo group had mild hypotension during study drug administration before clamping, which did not require intervention. Four patients (two in each group) had bradycardia during study drug administration before clamping, which did not require treatment. No differences between the two groups were noted with respect to the need for defibrillation to restore regular rhythm at the end of CPB (40/98 [40%] *v* 49/102 [49%]; p = 0.32) in the intermediate-risk population. Temporary pacing after CPB was used in 58% versus 67% patients (p = 0.34), with ventricular pacing used in 34% versus 36% (p = 0.93). Two patients in the placebo group experienced postoperative systolic anterior motion, which was treated medically without the need for a second pump run. After randomization, blood pressure, heart rate, pH, partial pressure of oxygen, partial pressure of carbon dioxide, and core temperature were similar in the two groups at all measured time points. The use of inotropic agents was similar at CPB weaning, but a significant reduction in the maximum vasoactive inotropic score during the first 24 postoperative hours was observed: ten (IQR 5-15) in the placebo group versus seven (IQR 5-10.5) in the esmolol arm (p = 0.04; risk difference [95% CI −2.1 {−4.4 to −0.1}]). The details on the use of inotropic agents in the ICU are shown in Table 3. Notably, the number of patients requiring norepinephrine in the first 24 hours (30% *v* 19%; p = 0.048) and the number of patients requiring epinephrine for more than 24 hours (22% *v* 11%; p = 0.040) were greater in the placebo group compared with the esmolol group.

Troponin peak occurred at ICU arrival for 11/200 patients (5%), at four hours for 126/200 patients (63%),

Table 2
Clinical Outcomes

| | Placebo Group(n = 98) | Esmolol Group(n = 102) | P Value | Risk Difference (95% CI) |
|---|---|---|---|---|
| Composite outcome, n (%) | 36 (37%) | 27 (26%) | 0.13 | −0.10 (−0.23 to 0.03) |
| Postoperative low cardiac output syndrome, n (%) | 13 (13%) | 6 (6%) | 0.08 | −0.03 (−0.13 to 0.8) |
| Postoperative IABP, n (%) | 18 (18%) | 16 (16%) | 0.60 | |
| Catecholamines for >48 h, n (%) | 17 (17%) | 10 (10%) | 0.12 | |
| Duration of mechanical ventilation (h), median (IQR) | 12 (10-18) | 12 (9-16) | 0.30 | |
| Mild pulmonary injury, n (%) | 31 (32%) | 27 (26%) | 0.40 | |
| Acute renal failure, n (%) | 19 (19%) | 12 (12%) | 0.17 | |
| Stage R, n (%) | 16 (16%) | 8 (8%) | 0.08 | |
| Stage I, n (%) | 2 (2%) | 4 (4%) | 0.68 | |
| Stage F, n (%) | 0 | 0 | 0.99 | |
| Stage L, n (%) | 0 | 0 | 0.99 | |
| Stage E, n (%) | 1 (1%) | 0 | 0.49 | |
| Ventricular fibrillation after CPB, n (%) | 40 (41%) | 49 (48%) | 0.32 | |
| Hospital stay (d), median (IQR) | 6 (5-9) | 6 (5-10) | 0.90 | |
| Ejection fraction ≥60% at discharge (%, mean ± SD) | 4/95 (4%) | 11/92 (12%) | 0.06 | |
| Serum creatinine at discharge (mg/dL, mean ±SD) | 0.88 ± 0.25 | 0.91 ± 0.29 | 0.28 | |
| Rate of hospital re-admission at 1 year, n (%) | 26/95 (27%) | 16/96 (17%) | 0.08 | |
| 30-d mortality, n (%) | 1 (1%) | 1 (1%) | 0.99 | |
| 1-y mortality, n (%) | 5/98 (5%) | 4/101 (4%) | 0.75 | |

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

Table 3
Need for Intraoperative and Postoperative Inotropic Support

| | Placebo Group(n = 98) | Esmolol Group(n = 102) | p Value | Risk Difference (95% CI) |
|---|---|---|---|---|
| Epinephrine at CPB weaning, n (%) | 82 (84%) | 76 (75%) | 0.11 | |
| Epinephrine maximum dose at CPB weaning (h), median (IQR) | 0.08 (0.05-0.1) | 0.07 (0.05-0.1) | 0.90 | |
| Epinephrine in the first postoperative 24 h, n (%) | 86 (88%) | 86 (85%) | 0.50 | |
| Epinephrine maximum dose in the first postoperative 24 h (μg/kg/min), median (IQR) | 0.08 (0.05-0.1) | 0.07 (0.05-0.1) | 0.79 | |
| Norepinephrine in the first postoperative 24 h, n (%) | 30 (31%) | 19 (19%) | 0.048 | |
| Norepinephrine maximum dose in the first postoperative 24 h (μg/kg/min), median (IQR) | 0.08 (0.05-0.15) | 0.1 (0.05-0.15) | 0.37 | |
| Epinephrine 24 h after surgery, n (%) | 21 (21%) | 11 (11%) | 0.040 | |
| Epinephrine maximum dose 24 h after surgery (μg/kg/min), median (IQR) | 0.1 (0.05-0.15) | 0.09 (0.05-0.15) | 0.80 | |
| Norepinephrine 24 h after surgery, n (%) | 9 (9%) | 0 | 0.002 | |
| Norepinephrine maximum dose 24 h after surgery (μg/kg/min), median (IQR) | 0.15 (0.05- 0.2) | 0 | / | |
| Maximum vasoactive inotropic score in operating room, median (IQR) | 8 (5-10) | 5 (3-10) | 0.13 | −1.2 (−3.1 to 0.8) |
| Maximum vasoactive inotropic score in the first postoperative 24 h, median (IQR) | 10 (5-15) | 7 (5-11) | 0.039 | −2.1 (−4.4 to −0.1) |
| Maximum vasoactive inotropic score 24 h after surgery, median (IQR) | 0 (0-2) | 0 (0-0) | 0.009 | −2.2 (−4.0 to −0.3) |

NOTE. Maximum dosage of each inotrope refers only to patient receiving the mentioned inotrope. Maximum vasoactive inotropic score is calculated overall, including patients not receiving inotropes.
Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; IQR, interquartile range.

and at 24 hours for 63/200 patients (32%). Troponin release was similar between the two groups (Table 4 and Fig. 2). Hospital stay was six days (IQR 5-9) in the placebo group and six days (IQR five-ten) in the esmolol group (p = 0.9). Upon discharge, serum creatinine did not differ between the two groups (0.88 ± 0.25 *v* 0.91 ± 0.29; p = 0.28). A trend toward an increase in the number of patients with an ejection fraction ≥60% upon discharge was reported in the esmolol group (4/95 [4%] *v* 11/92 [12%]; p = 0.06). Two (1%) patients (one in each group) died at 30-day follow-up, both of them in the ICU for multiple organ failure (p = 0.99). At one-year follow-up, 5/98 (5%) patients in the placebo group died, and 4/101 (4%) in the esmolol group died (p = 0.75), while a trend toward a reduction in the rate of hospital admission at one year in the esmolol group was observed (26/95 *v* 16/96; p = 0.08).

Table 4
Troponin T Levels

| | Placebo Group(n = 98) | Esmolol Group(n = 102) | p Value | Risk Difference (95% CI) |
|---|---|---|---|---|
| Troponin T at ICU arrival (ng/L), median (IQR) | 539 (347-827) | 479 (307-726) | 0.30 | |
| Troponin T at 4 h after surgery (ng/L), median (IQR) | 898 (598-1,203) | 754 (494-1,176) | 0.15 | |
| Troponin T at 1 d after surgery (ng/L), median (IQR) | 755 (501-1,192) | 652 (471-106) | 0.30 | |
| Troponin T at 2 d after surgery (ng/L), median (IQR) | 488 (328-747) | 471 (368-739) | 0.80 | |
| Troponin T peak (ng/L), median (IQR) | 968 (600-1,357) | 806 (607-1,299) | 0.30 | −165 (−592 to 262) |

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.

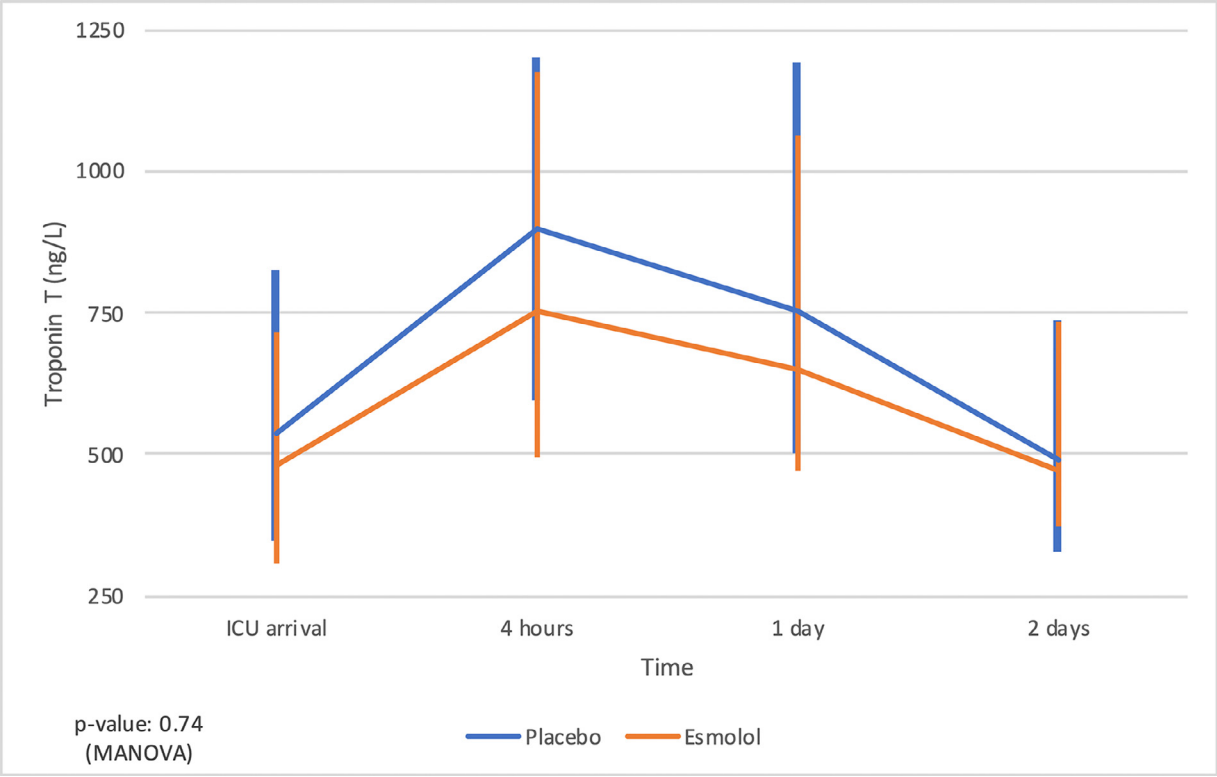


Fig. 2. Troponin T values at 0, 4, 24, and 48 hours in the placebo and esmolol groups. MANOVA.

## Discussion

Esmolol administration before aortic cross-clamping and as a cardioplegia adjuvant did not reduce a composite outcome of prolonged ICU stay and/or mortality in adult cardiac surgery, although it reduced the postoperative need for inotropic support. No adverse event or complication related to esmolol was recorded during the study. A trend toward a reduction in postoperative low-cardiac-output syndrome (13/98 *v* 6/102; p = 0.08), the rate of hospital admission at one year (26/95 *v* 16/96; p = 0.08) and a trend toward an increase in the number of patients with ejection fraction ≥60% at hospital discharge (4/95 *v* 11/92; p = 0.06) were observed.

The use of β-blockers in cardiac surgery has been debated.[18–20] If on the one hand the protective effects of β-blockers on myocardium (such as the reduction of heart oxygen consumption) could be beneficial,[16] on the other hand, the reduction of cardiac inotropism and chronotropism during CPB weaning and during the early postoperative period could be detrimental because myocardial stunning reaches its highest level a few hours after the end of CPB.[20]

In the perioperative setting of noncardiac surgery, the promising cardiac protective effects of β-blockers have not been confirmed. The POISE study showed that the acute use of extended-release metoprolol reduced perioperative ischemia in noncardiac surgery but increased the mortality rate and the incidence of stroke.[4]

Unlike long-acting agents, esmolol has a nine-minute half-life, and its metabolism mainly is based on erythrocytes esterase and only slightly influenced by organ function, boosting all the beneficial effects of β-blockers while reducing their side effects. Esmolol is used widely in the setting of cardiac intensive medicine, as medical treatment of arrhythmias,[21] ischemia,[22] and aortic dissection[23]; to improve microcirculation and oxygenation in critically ill patients experiencing sepsis or undergoing extracorporeal membrane oxygenation[24]; and a variety of other settings.[25] The use of esmolol as a cardioprotective agent during cardioplegic arrest finds a rationale because it could reduce the

oxygen demand of the heart by improving the imbalance between oxygen consumption and supply.[26]

In the literature, few groups have focused on the use of esmolol in cardiac surgery; however, small sample sizes did not allow for the study of clinically relevant endpoints, and findings are mixed.

Cork at al.[9] randomly assigned 30 patients (mostly undergoing coronary artery bypass surgery) in a double-blinded RCT to receive either esmolol (a bolus of 2 mg/kg followed by a continuous infusion of 0.3 mg/kg/min until ten minutes after removal of the aortic cross-clamp) or placebo. The esmolol group experienced a reduction in systemic lactate concentration, possibly implying a reduced ischemia rate.

Rinne at al.[10] performed an RCT in which esmolol was added to cold cardioplegia in patients undergoing urgent coronary revascularization. In this setting, esmolol supplementation failed to increase cardiac protection.

A meta-analysis of randomized trials involving the use of esmolol in cardiac surgery demonstrated significant reductions of myocardial ischemia ($p = 0.007$) and arrhythmias ($p = 0.05$) in patients treated with esmolol.[11]

The authors' group performed a pilot RCT[12] in a high-risk population with postoperative myocardial dysfunction (with LVEF <50% and LVEDD >60 mm) undergoing cardiac surgery. The authors adopted a different timing of administration and a different esmolol dosage compared with those of previous studies, administering esmolol before aortic cross-clamping and as cardioplegia adjuvant, as was done in the present study. The rationale behind this was that esmolol administration immediately after aortic cannulation may decrease the myocardial metabolic demand further, improving the protective effect of cardioplegia during aortic cross-clamping. A significant reduction of troponin T, confirming the cardioprotective properties of esmolol, was reported. However, findings were limited by the small sample size. To overcome this limit, a population of 200 moderate-risk patients undergoing cardiac surgery was included in the present trial, and the authors used the same timing of administration and dosage of esmolol and investigated clinically relevant endpoints. The present study's results showed that there were no differences in ICU stay and/or mortality between the two groups, and a significant reduction in cardiac troponin release was not confirmed. Interestingly, a significant reduction in the maximum vasoactive inotropic score during the first 24 postoperative hours was observed. A trend toward an increase of patients with normal ejection fraction (≥60%) on discharge also was reported in the esmolol group in the present trial. However, because the majority of the population was referred to surgery for mitral regurgitation, it is not surprising that only 8% of the population was discharged with a normal ejection fraction. In fact, in the context of severe mitral regurgitation, an ejection fraction of 55% to 60% (which is otherwise considered normal) already denotes pending left ventricular dysfunction. Although this finding did not have an effect on hard clinical outcomes in the present trial, a beneficial effect of esmolol cannot be ruled out and may become evident in larger clinical trials.

In subgroups analyses, patients with extreme preoperative cardiac conditions (severely dilated left ventricle and low ejection fraction) showed a trend toward a beneficial effect of esmolol. Additional studies should focus on this particular subset of patients because they are more prone to develop postoperative cardiac complications and might benefit the most from intraoperative esmolol administration. Although not investigated in the present trial, patients with severe left ventricular hypertrophy also may benefit from esmolol administration and should be investigated in future trials. The role of perioperative β-blockers also might be interesting; in fact, although no statistically significant differences were reported, esmolol seems to have a greater effect in patients not on preoperative β-blockers. This preliminary finding needs further investigation and may be the subject of future studies in the field.

The present study had strengths and limitations. This work reports the results of a single-center trial led in a tertiary care center that is a national referral center for cardiac surgery, especially for mitral valve repair, with low mortality rates. Therefore, the case mix differed from that of most other cardiac surgery centers, with more valvular surgeries and relatively fewer coronary artery bypass procedures.[27] The limitations of single-center trials are well-known[28]; nevertheless, the present study's results are relevant and will guide additional multicentric studies to focus on patients who may benefit more from esmolol administration (eg, extremely dilated or dysfunctional left ventricle). In addition, there is still no agreement about the best timing and route of administration of esmolol in the literature. The authors acknowledge that they did not collect some important postoperative data (eg, the rate of postoperative atrial fibrillation). The authors chose their method on the basis of their previously published promising results. Moreover, there was a mismatch between the expected and observed rate of the primary endpoint, leading to a possible underpowered study to assess for clinically relevant outcomes. Technical advances over the last decade have improved outcomes in cardiac surgery dramatically, thus reducing the rate of prolonged ICU stay and perioperative mortality. At the same time, many factors may have affected the primary outcome on top of the double administration of the short half-life esmolol used in the present study. Furthermore, delta inflation may have played a role in overestimating treatment effect size during the design of the present trial.[29] The role of the vasoactive inotropic score in cardiac surgery still is debated, but its importance in predicting outcomes and to allow comparisons among studies is not out of the question.[30] It also is worth noting that preoperative β-blockers were restarted as early as possible in the postoperative period in all study patients. This might have acted as a confounder, limiting the magnitude of the study's findings because both groups were exposed in some extent to β-blockers. That being said, the present study was the largest randomized trial ever performed on esmolol in cardiac surgery, and its findings are relevant—considering that esmolol is cheap and widely available—and require further investigation.

## Conclusion

Esmolol administration did not reduce a composite outcome of prolonged ICU stay and/or mortality compared with placebo in adult cardiac surgery. However, a significative reduction in the need for inotropic support and trends toward the reduction of postoperative low-cardiac-output syndrome and a beneficial effect in "extreme" preoperative heart conditions may suggest a role for esmolol in enhancing postoperative cardiac performance. Additional multicenter trials are needed to assess the role of esmolol, especially in patients with preoperative left ventricular hypertrophy or severely impaired left ventricular function.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2020.12.029.

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