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ORIGINAL RESEARCH

Esmolol as a cardioprotective agent to reduce low cardiac output syndrome after cardiac surgery

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Abstract

Early postoperative left ventricular dysfunction due to myocardial stunning can negatively affect outcomes in patients with mitral regurgitation undergoing mitral valve surgery. The aim of this study was to evaluate the impact of the ultra-short acting β-blocking agent esmolol, administered after the anesthesia induction and before aortic cross-clamping, on myocardial protection and on postoperative clinical course in patients undergoing mitral valve surgery for mitral regurgitation. Patients undergoing mitral valve surgery for primary mitral regurgitation were analyzed according to the use or not of esmolol. Clinical, procedural and laboratory data were collected. A 1:2 propensity score matching analysis (esmolol *vs.* control) was performed to adjust for baseline differences. The primary endpoint was the occurrence of postoperative low cardiac output syndrome. Out of 322 patients (age: 66 $\pm$ 11 years; 140 women) with mitral regurgitation undergoing mitral valve surgery, 99 received esmolol while 223 patients did not. Low cardiac output syndrome occurred significantly less frequently in patients treated with esmolol as compared to patients not receiving it (12.1% *vs.* 33.2%, $p <$ 0.001 before matching and 13.0% *vs.* 30.4%, $p = 0.006$ after matching). Peak post-procedural creatin kinase MB release was lower in patients treated with esmolol as compared to those not treated with esmolol (57 $\pm$ 30 μg/mL *vs.* 82 $\pm$ 70 μg/mL, $p <$ 0.001 before matching and 57 $\pm$ 31 μg/mL *vs.* 83 $\pm$ 79 μg/mL, $p = 0.008$ after matching). Acute kidney injury and length of intensive care unit stay were reduced in the esmolol group both before and after matching. In conclusion esmolol administered after anesthesia induction and before aortic cross-clamping could improve myocardial protection in patients with mitral regurgitation undergoing mitral valve surgery.

Keywords

Anesthesia; Esmolol; β-blockers; Cardiac surgery; Mitral valve surgery; Low cardiac output syndrome; Intensive care

1. Introduction

Mitral valve surgery (MVS) represents the standard of care for patients with mitral regurgitation (MR) and is performed in over 20,000 patients in the United States each year [1].

Early postoperative left ventricular (LV) dysfunction can negatively affect early and long-term survival in patients undergoing MVS [2–5]. Early LV dysfunction is observed in up to 30% of patients undergoing MVS [5]. Of note, LV dysfunction may also occur among patients with preserved systolic function before surgery (LV end-systolic diameter $\leq$35 mm and LV ejection fraction $>$60%) immediately after the separation from cardiopulmonary bypass (CPB) or later in the post-operative phase [5]. The occurrence of this complication requires inotropic or mechanical support for 48 to 72 hours after surgery to avoid the harmful consequences of low cardiac output syndrome (LCOS). LCOS is in fact associated with increased mortality, morbidity and length of hospital stay [6].

The main causes of post-operative LV dysfunction are generally considered to be the unmasking of preoperative ventricular dysfunction, afterload mismatch, and myocardial stunning. While the first two have been widely studied [2–5, 7, 8], limited evidence is available on myocardial stunning, particularly in the setting of surgery for MR.

Myocardial stunning is defined as the myocardial dysfunction that follows brief ischemic events, typically resolves in 48 to 72 hours [9–12], and is frequently observed after aortic cross-clamping with cardioplegic arrest. Preventing this event represents a major challenge after cardiac surgery. The use of esmolol before or during CPB was associated with cardioprotective effects by reducing the potential ischemia-reperfusion injury in small randomized studies on patients undergoing elective cardiac surgery [13, 14] and landiolol was associated with reduced mortality in a large observational

study performed in Japan in the same setting [15]. Cardiac biomarkers like creatine kinase MB isoenzyme (CK-MB) and cardiac troponin I (cTnI) are predictors of poor outcome after cardiac surgery [16] and short acting β-blockers are likely reducing cardiac damage and cardiac biomarkers release [13, 14, 17].

In this study we evaluated the cardioprotective effect of esmolol administered after anesthesia induction and prior to aortic cross-clamping in reducing LCOS in patients undergoing MVS for MR.

2. Methods

2.1 Study population

This observational data collection was performed over a two-year period in patients undergoing MVS (repair or replacement), for primary MR with or without other cardiac surgery procedures. Exclusion criteria were functional or ischemic MR, mitral stenosis, preoperative dialysis, hepatic dysfunction, age $<$18 years, history of side effects from β-blockers, need for emergency surgery, and refusal or inability to sign informed consent. Patients taking β-blockers as part of their regular therapeutic regimen were not excluded from the study.

Patients were analyzed according to having received or not the ultra-short acting β-blocker agent esmolol after anesthesia induction and before aortic cross-clamping.

2.2 Aims

The aim of this study was to determine whether administering esmolol after anesthesia induction and before aortic cross-clamping in patients undergoing MVS for MR would reduce the incidence of LCOS.

2.3 Esmolol use

Different esmolol dosages have been proposed for various hospital settings including but not limited to perioperative care and critically ill patients [18]. We administered a total dose of intravenous esmolol of 10 mg/kg, starting with a continuous infusion of 300 μg/kg/min after anesthesia induction followed by a bolus of the remaining dose (up to 10 mg/kg) after the onset of CBP and before aortic cross-clamping. Esmolol was continued if the heart rate was $\geq$40 bpm, systolic arterial blood pressure was $\geq$80 mmHg, and there was no evidence of third-degree atrio-ventricular block. If these events occurred, esmolol was paused, and the effect reversed by infusion of β-adrenergic agonists. The infusion of esmolol was promptly restarted when systolic arterial pressure $\geq$80 mmHg and heart rate $\geq$40 bpm.

2.4 Data collection

Clinical, procedural and laboratory data were entered into a dedicated database. Clinical data included patients' demographics, medical and surgery history, baseline cardiac status, and perioperative data.

2.5 Study endpoints and definitions

2.5.1 Low cardiac output syndrome

The primary endpoint was to document the effect of esmolol on the reduction of LCOS defined by the presence of tachycardia, hypotension requiring intra-aortic balloon pump and/or inotropic support for greater than 24 hours ($>$dopamine 5 μg/kg/min or norepinephrine and epinephrine $>$0.05 μg/kg/min), and impaired end-organ perfusion associated with central venous oxygen saturation less than 65%, metabolic acidosis (decrease in base deficit $>$4) or serum lactate level higher than 2.9 mmol per liter in the absence of a cause other than heart failure [19].

2.5.2 Secondary outcomes

Peak serum level of CK-MB and cTnI, operative mortality, postoperative renal failure, time of mechanical ventilation, and length of stay in intensive care unit were collected.

Operative mortality was defined as death within 30 days of surgery, whether in or out of hospital, or death in-hospital regardless of length of hospital stay.

Postoperative renal failure was assessed by determining daily serum creatinine measurements during the entire hospital stay. Based on the RIFLE criteria [20], postoperative renal failure was defined as mild in case of $\geq$50% increase of serum creatinine, and as severe in case of $\geq$100% increase of serum creatinine (or need for hemodialysis) as compared to preoperative values.

CK-MB and cTnI concentrations were determined in venous blood samples the day before surgery, at arrival in intensive care unit after surgery, after additional 4 hours, and daily thereafter through 5 days.

In our center the indications for tracheostomy included either two failed extubations or intubation for more than 10 days.

2.6 Anesthesiological management and surgical technique

Patients were managed in accordance with the institution's standard practice for cardiac surgery. Patient monitoring included invasive radial artery blood pressure measurement, continuous electrocardiographic leads II and V5 monitoring with ST-segment monitoring, pulse oximetry, central venous pressure, capnometry, urinary output, and transesophageal echocardiography. MVS was performed through standard sternotomy or using a minimally invasive approach (*i.e.*, right lateral thoracotomy) [21–24]. Crystalloid cardioplegia (Custodiol®, Dr Franz Köhler CHemie GMBH, Bensheim, Germany) was employed in all patients. Cardiopulmonary bypass was conducted under normothermia with a flow target of 2.5 L/min/m^2. Valve repair was performed with a variety of surgical techniques according to valve anatomical and functional characteristics. Discontinuation from cardiopulmonary bypass was performed under transesophageal echocardiography monitoring. Following optimization of volume and rhythm, ventricular dysfunction and hypotension were managed with epinephrine, whereas situations of ventricular dysfunction and normotension were managed with enoximone. In the event of persistent hypotension with good ventricular function, norepinephrine was employed. Following the surgical procedure, patients were transferred

to the intensive care unit and sedated with propofol at a rate of 2 mg/kg/h. Ventilation was discontinued once the patient demonstrated hemodynamic stability, absence of significant bleeding, normothermia and an adequate level of consciousness and pain control. Intravenous morphine was administered to all patients for postoperative pain management.

2.7 Statistical analysis

Baseline clinical and procedural characteristics as well as clinical outcomes were compared between groups. Continuous data are presented as median values, whereas dichotomous data are presented as percentages. Differences between groups were evaluated by Wilcoxon's nonparametric test or χ^2 test without Yates' correction for continuity or the Fisher exact test as appropriate. Differences between groups in terms of event rates were evaluated by χ^2 test or Fisher's exact test, whichever was appropriate.

Forward logistic regression was used to assess the independent correlates of LCOS. Multivariable analysis was performed through logistic regression with forward stepwise selection that incorporated the following variables: age, diabetes, chronic kidney disease, previous valvular surgery, New York Heart Association (NYHA) class III–IV, ischemia time, LV ejection fraction, hematocrit, creatinine clearance, EuroScore I, and esmolol use, with LCOS as independent variable. Findings of this analysis are presented as odds ratio and 95% confidence interval.

Propensity score matching was used to account for possible differences in baseline characteristics between groups. The propensity scores for receiving esmolol were estimated using a probit model, including age, left ventricular ejection fraction, creatinine clearance and pre-treatment variables associated with esmolol treatment in the multivariable model at p-value < 0.10 as independent variables (indexed left ventricular diastolic volume and age). The propensity score is the probability that a patient would have been treated with esmolol given the patient's observed pre-treatment characteristics. Observations matched on the basis of the propensity scores using a conservative caliper are likely to have comparable distributions of baseline characteristics. To determine whether this assumption of balanced baseline characteristics was satisfied, we used standard comparison tests (unpaired t test and Fisher's exact test). To match patients, we used an automated matching procedure in the software package that randomly selected a patient treated with esmolol and a randomly selected patient not treated with esmolol from the pool of potential patients with propensity scores within a caliper of ± 0.05 on the propensity score. Successfully matched pairs were removed, and the procedure repeated until all patients treated with esmolol were matched to two comparators or until no further patients not treated with esmolol were available within the caliper.

Statistical analyses were performed using SPSS (version 23, SPSS, Inc., Chicago, IL, USA), and Stata (version 13.1, Stata Corp., College Station, TX, USA).

3. Results

The study flow is summarized in Fig. 1. During the study period, 329 consecutive patients underwent MVS (repair or replacement) for primary MR and 322 were included in the study (99 patients received esmolol before aortic cross-clamping, while 223 patients did not receive it). As summarized in Table 1, baseline clinical characteristics and procedural variables were similar between the two groups even before the propensity matching.

Pre-specified primary and secondary outcomes of interest in the overall cohort are reported in Table 2 and Fig. 2. We observed a lower rate of LCOS in patients treated with esmolol as compared to patients not treated with esmolol (12.1% *vs.* 33.2%, $p < 0.001$). Peak post-procedural myocardial enzymes values were lower in patients treated with esmolol as compared to those not treated with esmolol (cTnI 17.1 $\pm$ 12.2 μg/mL *vs.* 24.8 $\pm$ 32.1 μg/mL, $p = 0.021$; CK-MB 57 $\pm$ 30 μg/mL *vs.*

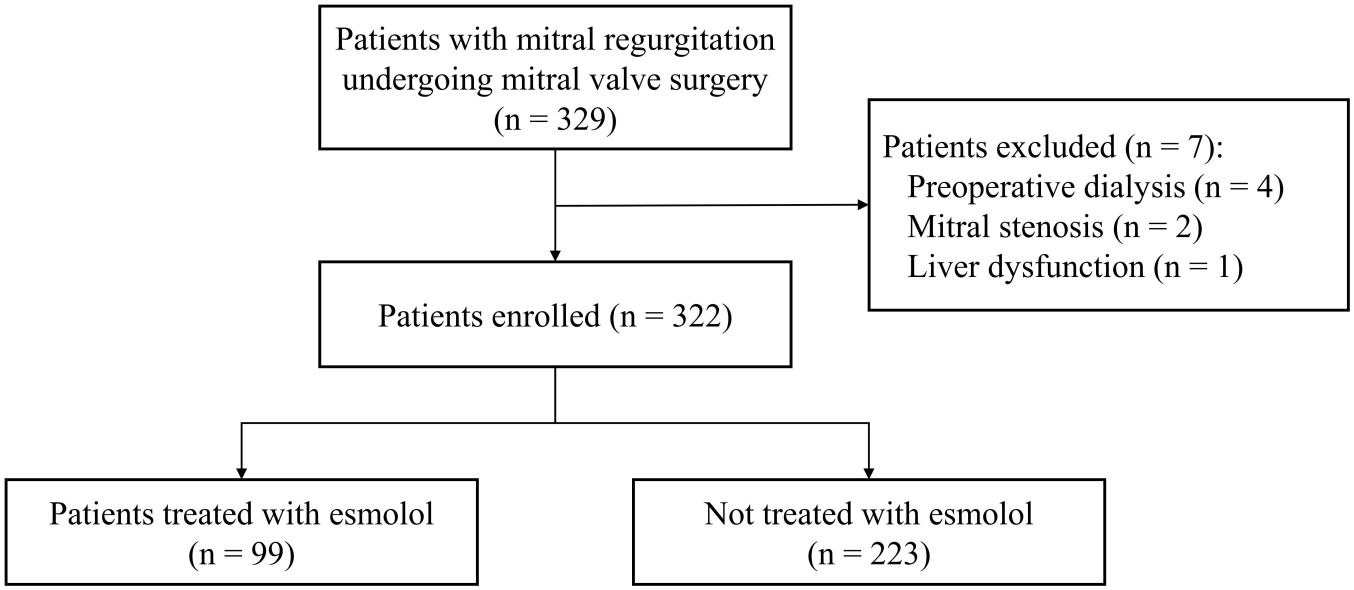

FIGURE 1. Study flowchart.

TABLE 1. Baseline clinical characteristics and procedural variables.

	Overall cohort			Propensity matched analysis		
	Esmolol (N = 99)	Control (N = 223)	*p*-value	Esmolol (N = 69)	Control (N = 138)	*p*-value
Age (yr)	65 ± 12	66 ± 11	0.490	66 ± 12	65 ± 11	0.321
Female	50 (50.5%)	90 (40.4%)	0.090	35 (50.7%)	80 (58.0%)	0.374
Clinical presentation						
LV ejection fraction	59 ± 9	58 ± 9	0.439	59 ± 9	59 ± 9	0.954
Body mass index	25.2 ± 3.6	25.3 ± 4.3	0.800	25.2 ± 3.9	25.2 ± 4.0	0.954
NYHA 3–4	52 (52.5%)	133 (59.6%)	0.233	35 (50.7%)	79 (57.2%)	0.379
Logistic Euroscore	6 ± 6	6 ± 7	1.000	6 ± 4	5 ± 4	0.227
Comorbidities						
Diabetes on treatment	10 (10.1%)	30 (13.5%)	0.400	7 (10.1%)	17 (12.3%)	0.819
COPD	9 (9.1%)	17 (7.6%)	0.656	4 (5.8%)	11 (8.0%)	0.778
Cerebrovascular accident	5 (5.1%)	7 (3.1%)	0.524	2 (2.9%)	4 (2.9%)	0.999
Hypertension on treatment	45 (45.5%)	123 (55.2%)	0.108	34 (49.3%)	71 (51.4%)	0.771
Active endocarditis	3 (3.0%)	8 (3.6%)	1.000	2 (2.9%)	7 (5.1%)	0.721
Peripheral artery disease	5 (5.1%)	9 (4.0%)	0.768	5 (7.2%)	7 (5.1%)	0.539
Chronic kidney disease	10 (10.1%)	26 (11.7%)	0.682	7 (10.1%)	15 (10.9%)	0.873
Previous valve procedure	9 (9.1%)	19 (8.5%)	0.867	4 (5.8%)	9 (6.5%)	0.839
Baseline laboratory values						
Hemoglobin (g/dL)	13.1 ± 1.6	12.7 ± 1.8	0.116	13.1 ± 1.5	12.9 ± 1.7	0.372
Creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.3	0.668	1.1 ± 0.3	1.0 ± 0.3	0.699
Creatinine clearance (mL/min)	66.8 ± 27.1	63.0 ± 32.4	0.311	64.8 ± 26.6	68.1 ± 32.1	0.459
Echocardiographic parameters						
LV EDD (mm)	55.2 ± 8.4	56.5 ± 8.5	0.468	55.1 ± 6.2	55.9 ± 8.2	0.658
LV ESD (mm)	34.4 ± 8.6	36.9 ± 8.1	0.197	35.6 ± 7.9	36.2 ± 7.3	0.763
LV EDV/BSA	76.6 ± 19.4	82.0 ± 22.9	0.085	76.8 ±19.9	81.8 ± 23.2	0.123
LV ESV/BSA	31.7 ± 16.2	34.9 ± 19.3	0.512	32.4 ± 16.3	32.1 ± 15.3	0.923
Chronic Medications						
ACE inhibitors	34 (34.3%)	95 (42.6%)	0.163	27 (39.1%)	62 (44.9%)	0.427
Beta blockers	56 (56.6%)	137 (61.4%)	0.411	41 (59.4%)	85 (61.6%)	0.763
Diuretics	63 (63.6%)	151 (67.7%)	0.475	41 (59.4%)	90 (65.2%)	0.415
Isolated mitral surgery						
Sternotomy	60 (60.6%)	127 (57.0%)	0.198	41 (59.4%)	80 (58.0%)	0.434
Thoracotomy	9 (9.1%)	11 (4.9%)		7 (10.1%)	8 (5.8%)	
Associated surgical procedures	30 (30.3%)	85 (38.1%)	0.189	21 (30.4%)	50 (36.2%)	0.407
Ischemia time (min)	79 ± 23	82 ± 32	0.179	79 ± 25	87 ± 31	0.324

Values are expressed as mean ± SD or N (%) as appropriate.
ACE: Angiotensin-Converting Enzyme; BSA: body surface area; COPD: chronic obstructive pulmonary disease; EDD: end-diastolic diameter; EDV: end-diastolic volume; ESD: end-systolic diameter; ESV: end-systolic volume; LV: left ventricle; NYHA: New York Heart Association.

TABLE 2. Primary and secondary outcomes.

	Overall cohort			Propensity matched analysis		
	Esmolol (N = 99)	Control (N = 223)	*p*-value	Esmolol (N = 69)	Control (N = 138)	*p*-value
LCOS	12 (12.1%)	74 (33.2%)	<0.001	9 (13.0%)	42 (30.4%)	0.006
Mild AKI	17 (17.2%)	76 (34.1%)	0.002	14 (20.3%)	47 (34.1%)	0.041
Severe AKI	3 (3.0%)	36 (16.1%)	<0.001	2 (2.9%)	21 (15.2%)	0.008
Hemodialysis	1 (1.0%)	9 (4.0%)	0.294	1 (1.4%)	3 (2.2%)	0.999
Peak cardiac enzymes						
cTnI (µg/mL)	17.1 ± 12.2	24.8 ± 32.1	0.021	16.9 ± 12.5	24.8 ± 33.2	0.060
CK-MB (µg/mL)	56.9± 30.2	82.0 ± 70.5	<0.001	57.1 ± 31.0	83.4 ± 78.7	0.008
Ventilation time (h)	30.7 ± 55.5	75.9 ± 199.6	0.027	27.2 ± 46.2	69.5 ± 190.7	0.071
Tracheostomy	2 (2.0%)	10 (4.5%)	0.356	0 (0.0%)	6 (4.3%)	0.182
ICU stay (d)	3.2 ± 3.4	6.1 ± 9.9	0.005	3.0 ± 2.9	5.6 ± 9.7	0.032
Mortality	3 (3.0%)	14 (6.3%)	0.289	2 (2.9%)	4 (2.9%)	0.999

Values are expressed as mean ± SD or N (%) as appropriate.
AKI: acute kidney injury; cTnI: cardiac troponin I; CK-MB: creatin kinase MB; ICU: intensive care unit; LCOS: low cardiac output syndrome.

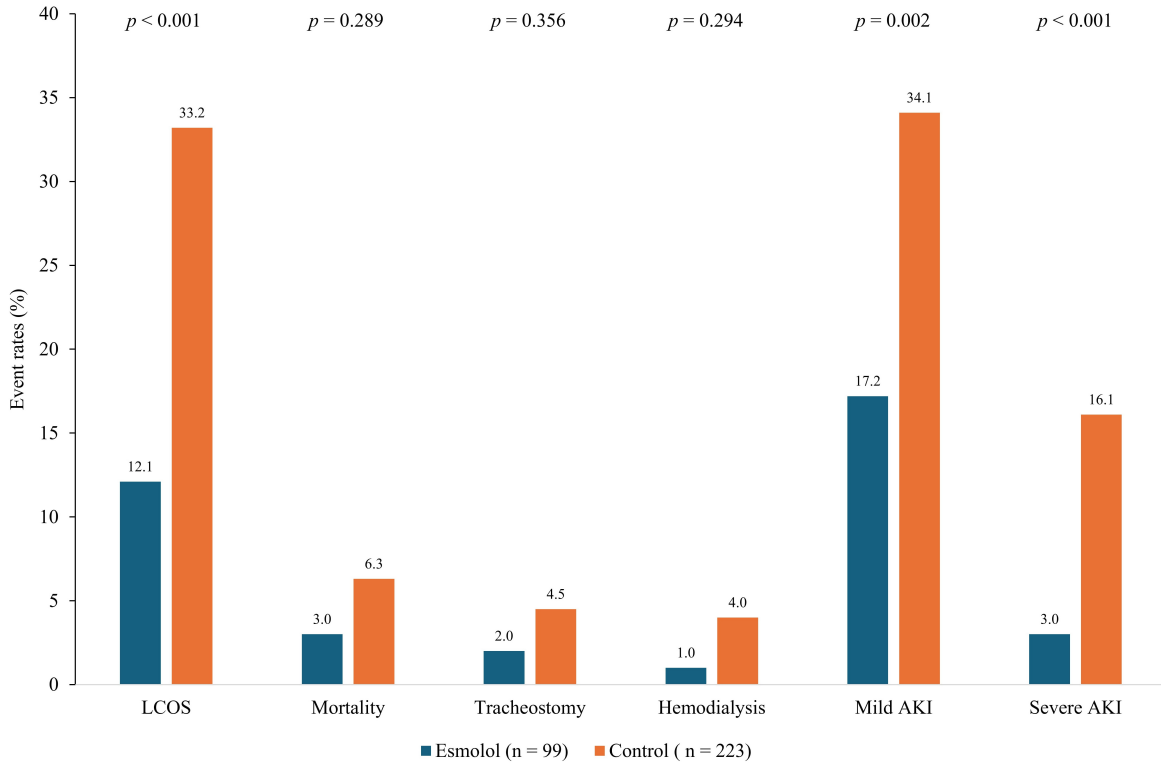

FIGURE 2. Clinical outcomes. AKI: acute kidney injury; LCOS: low cardiac output syndrome.

82 ± 70 µg/mL, $p < 0.001$). Patients treated with esmolol as compared to those not treated with esmolol experienced less frequently mild (17.2% *vs.* 34.1%, $p = 0.002$) and severe (3.0% *vs.* 16.1%, $p = 0.001$) acute kidney injury, had shorter intensive care unit stay (3.2 ± 3.4 days *vs.* 6.1 ± 9.9 days, $p = 0.005$), and had shorter ventilation time (31 ± 55 hours *vs.* 76 ± 199 hours, $p = 0.027$). Rates of mortality (3.0% *vs.* 6.3%, $p = 0.289$), need for tracheostomy (2.0% *vs.* 4.5%, $p = 0.356$), and hemodialysis (1.0% *vs.* 4.0%, $p = 0.294$) did not differ between groups.

As shown in Fig. 3, the multivariable analysis identified esmolol use as a strong independent predictor of LCOS prevention (odds ratio 4.06, 95% confidence interval 1.93–8.54).

The results of the subgroup analyses showed no significant between group differences for sex, age and surgical approach (Fig. 4).

After propensity score matching (1:2), (69 patients treated with esmolol *vs.* 138 patients who did not receive esmolol) (Table 2 and Fig. 2) LCOS rates were confirmed lower in patients treated with esmolol as compared to patients not treated

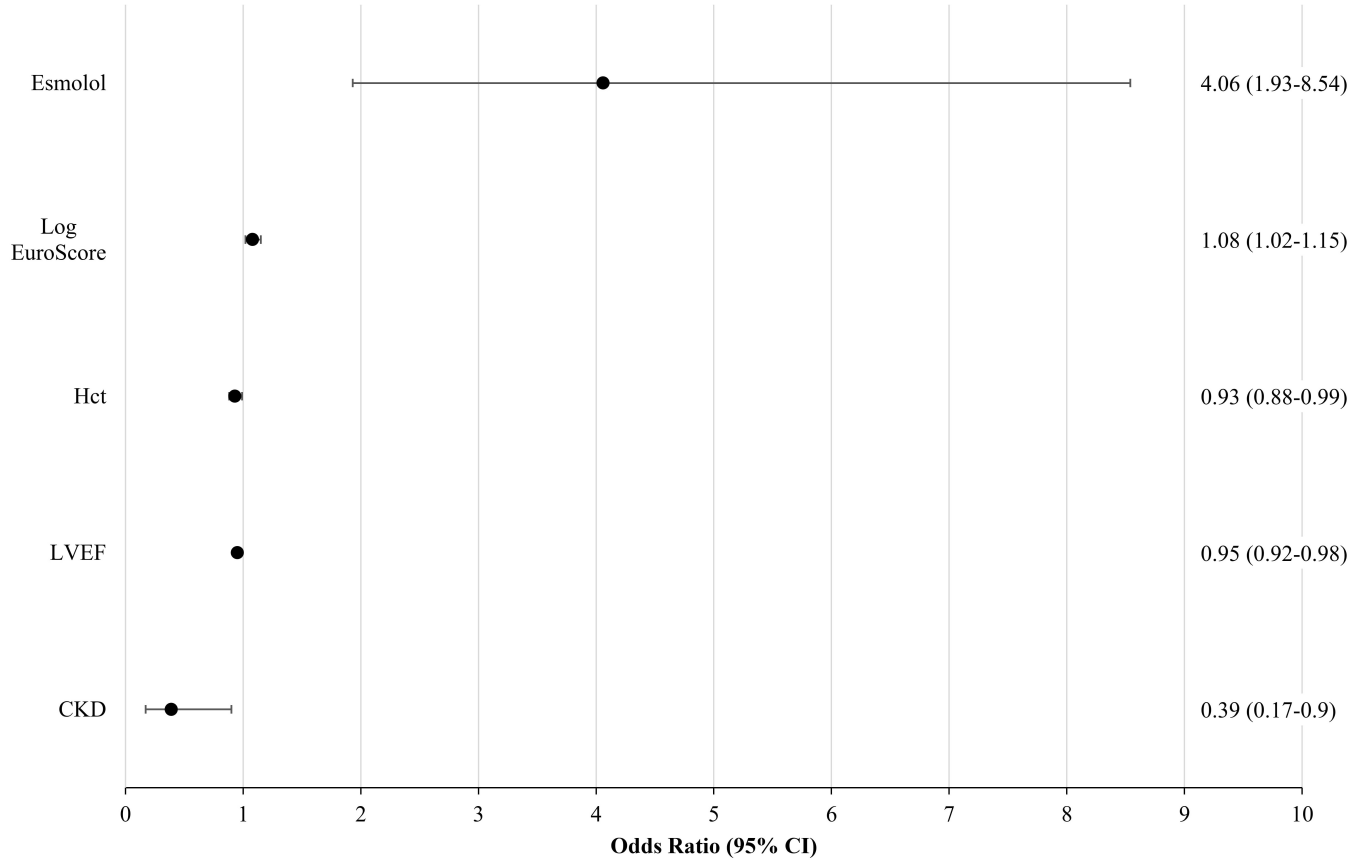

FIGURE 3. Predictors of low cardiac output syndrome prevention. Independent predictors of Low Cardiac Output Syndrome (LCOS) prevention at multivariate analysis. CI: confidence interval; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; Hct: hematocrit.

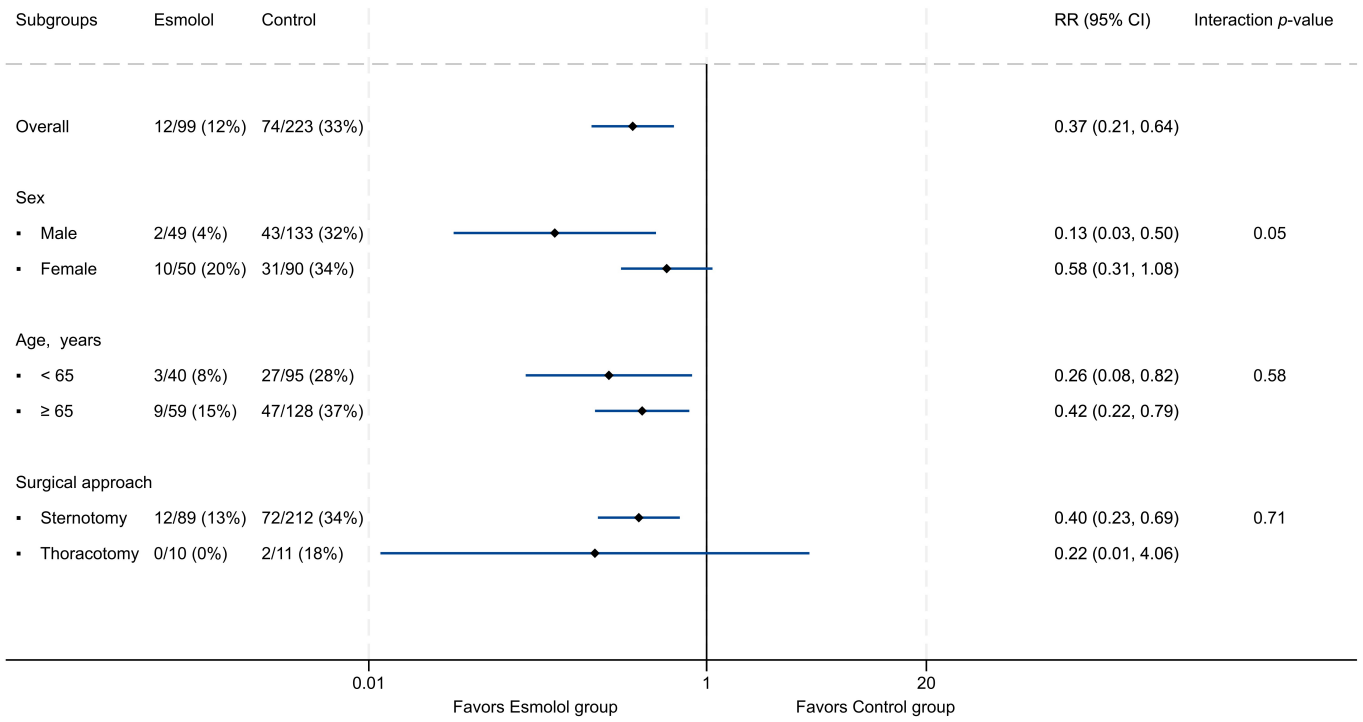

FIGURE 4. Subgroup analyses for the primary outcome. CI: confidence interval; RR: relative risk.

with esmolol (17.6% *vs.* 30.4%, p = 0.006). Peak post-procedural myocardial enzymes values were lower in patients treated with esmolol as compared to those not treated with esmolol, although the difference in terms of cTnI was no more significant after propensity-score matching (cTnI 17 ± 12.5 μg/mL *vs.* 24.8 ± 33.1 μg/mL, p = 0.060; CK-MB 57 ± 31 μg/mL *vs.* 83 ± 78 μg/mL, p = 0.008). Patients treated with esmolol as compared to those not treated with esmolol experienced less frequently mild (20.3% *vs.* 34.1%, p = 0.041) and severe (2.9% *vs.* 15.2%, p = 0.009) acute kidney injury, and had shorter intensive care unit stay (3.1 ± 3 days *vs.* 5.6 ± 9.6 days, p = 0.032). There was no difference in terms of ventilation time (27 ± 46 hours *vs.* 69 ± 191 hours, p = 0.071), mortality (2.9% *vs.* 2.9%, p = 0.999), need for tracheostomy (0% *vs.* 4.3%, p = 0.079), and hemodialysis (1.4% *vs.* 2.2%, p = 0.721) between groups.

4. Discussion

The main finding of this study is that esmolol administration before cardioplegic arrest appears to exert cardioprotective effects and to reduce the rate of postoperative LCOS, both in the overall and in the propensity score matched cohorts.

Surgical correction of MR is associated with a high incidence of postoperative LV dysfunction [2–5]. Several lines of evidence indicate that poor outcomes after surgery for MR might be due to an underestimation of the true degree of LV dysfunction at the time of surgery [25]. As a matter of fact, an LV ejection fraction inferior to 60% in the setting of severe MR represents a significant LV dysfunction and predicts poor outcomes after surgery [8]. Early surgical techniques—such as resection of the subvalvular apparatus—also contributed to unfavorable postoperative outcome by impairing LV systolic performance after MV replacement. Moreover, once mitral competence is restored, the low pressure outlet for LV is removed and the enlarged LV must eject entirely into the aorta with the subsequent result of increasing afterload [7, 24, 26]. It is, therefore, not surprising that the systolic performance of the LV often declines after surgical correction of MR.

A number of reports addressing LV contractile function after mitral surgery suggested that the elimination of severe, chronic MR may predispose patients with impaired preoperative LV contractility to cardiac dysfunction postoperatively [27]. Notwithstanding, also patients with normal LV systolic function prior to surgery may develop postoperative LV dysfunction requiring inotropic support and even intra-aortic balloon assistance (IABP) [5]. The latter indicates that—despite efforts directed at myocardial protection—intraoperative injury remains a relevant issue in patients undergoing MVS [28, 29].

The findings of this study show that intravenous esmolol administration before cardioplegic arrest may have an important cardioprotective role, as indicated by a marked reduction in the rate of LCOS and by a reduction in the postoperative release of the cardiac biomarkers CK-MB and cTnI. Of note, postoperative increase in CK-MB and cTnI levels has been associated with impaired short- and long-term clinical outcomes after MVS [30]. Lower levels of CK-MB and cTnI may reflect a better myocardial protection during cardioplegic arrest in patients undergoing MV surgery for MR. Similar cardioprotective effects have been previously described with β-blocker administration in patients percutaneous coronary intervention [31] and cardiac surgery [13, 14, 32, 33] and they are currently being studied [34]. The cardioprotective effects of esmolol were paralleled by consistent clinical benefits as indicated by a reduced risk of postoperative acute kidney injury, and by shorter ventilation time and intensive care unit stay.

The mechanism through which esmolol exerts its cardioprotective effects during global ischemic arrest is partially unclear [35–37]. The pre-ischemic state of myocardium can influence the degree of stunning that follows an ischemic event. Esmolol effective reduction in myocardial work and oxygen demand before cardioplegic arrest may permit the heart to better tolerate the subsequent global ischemia by promoting the preservation of myocardial energy reserve that alleviates myocardial stunning [38]. The subsequent cessation of electrical and mechanical activity at the time of cardioplegia results in less anaerobic metabolism, oxygen consumption, adenosine triphosphate (ATP) hydrolysis, and thereby less generation of hydrogen ions, which contribute to the degree of postoperative stunning. Thus, esmolol can minimize anaerobic myocardial metabolism and promote the preservation of myocardial energy reserves, resulting in better myocardial protection and post-CPB cardiac function [39]. Other pharmacologic actions attributed to esmolol, particularly at high doses, include improved membrane stabilization, decreased intracellular lipase activity, reduction of calcium influx and fatty acid injury following reperfusion [35, 40]. In addition, esmolol appears to be associated with lower systemic and coronary sinus lactate levels after removal of the aortic cross-clamp [39]. Finally, β-blockers may improve postoperative cardiac function through apoptotic myocardial cell death reduction [41]. High catecholamine concentrations are cytotoxic to cardiac myocytes and cardiac surgery is accompanied by a 2- to 20-fold increase of serum catecholamines levels. Because apoptotic cell death occurs within a few hours, apoptosis may be an important mechanism for loss of viable cardiomyocytes and myocardial dysfunction in the immediate perioperative period. Esmolol has the potential to counteract this phenomenon through an ultra-short acting β-adrenergic antagonism with a rapid onset and short duration of action. Ultra short acting β-blockers are also well known for their effect on prevention of postoperative atrial fibrillation after cardiac surgery [42–48].

The present study is subject to the inherent limitations of a nonrandomized design. Therefore, these results should, be considered hypothesis-generating and will require validation through a randomized controlled trial on the clinical effects of esmolol in patients with MR undergoing MVS. Another limitation of our study is the absence of data on antioxidant and biomarker levels, which prevents a precise evaluation of ischemia-reperfusion damage. Additionally, we did not collect data on the use of vasopressors, inotropes and fluid balance, factors that could have impacted the development of LCOS. Furthermore, we acknowledge that the inclusion of patients on chronic β-blocker treatment may have diminished the intervention's effect size. Nevertheless, our results are strengthened, and potential study design bias is minimized by

the inclusion of a large number of patients with broad inclusion criteria and minimal exclusion criteria, and by the similar baseline risk profiles between groups without the need for any adjustment.

5. Conclusions

The findings of the present study demonstrate a reduction in the incidence of LCOS in patients treated with esmolol. This suggests that administering esmolol after anesthesia induction and before aortic cross-clamping may improve myocardial protection in patients with MR undergoing MVS.

AVAILABILITY OF DATA AND MATERIALS

Deidentified participant data will be made available one year after publication upon submission of an appropriate research question, approval of the application by all the study authors, and execution of a data sharing agreement. Any relevant inquiries for the data sharing should be sent to the corresponding author via email.

AUTHOR CONTRIBUTIONS

GC and GL—contributed to the study conception or design and have directly assessed and verified the data reported in the manuscript. LT, MDP, FC, CR and FMO—contributed to the acquisition, analysis, or interpretation of data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Institutional Review Board of Ospedali Riuniti di Ancona in June 2013 (approval number: 213383 D.G. 560). Informed consent was obtained from all patients enrolled in the study.

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Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as the Editor-in-Chief of this journal. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

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