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Outcome of esmolol potassium cardioplegia compared to potassium cardioplegia in patients with solitary valvular disease

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Abstract
Perioperative myocardial damage still one of the main serious complications of cardiac surgery, many factors have been involved through the pathogenesis procedure, involving the technique of cardiac surgery, creation of cardioplegia and duration of cardiac arrest (1, 2). It has been well reported that precocious management of beta-adrenergic antagonist through cardiopulmonary bypass (CPB) or during ten minutes following liberation of aortic clamp participates to left ventricular function (3, 4). In addition, cardioplegia included esmolol, an ultra-short-acting (9-minute half-life) cardioselective beta blocker, has cardioprotection in animal model and clinical clients (5, 6). Esmolol, an ultra-short-acting beta-blocker, is recognized to reduce myocardial ischemia-reperfusion damage. The purpose of this investigation was carried out to compare the impacts of esmolol and potassium on myocardial metabolism through hypothermic blood cardioplegia employing lactate level in the coronary sinus as a marker. Eighty patients , with mean age of esmolol group was 39.5 while that of the control group was 37.58,operated on for solitary valvular disease were randomly designated to persistent coronary infusion with either potassium or esmolol through cardiopulmonary bypass. All patients assigned into two groups, group A as esmolol group as and group B as control group .Myocardial metabolism was assessed by serial coronary sinus lactate level via retrograde cardioplegia cannula was derived to assess the effect of esmolol as indicator of myocardial ischemia before aortic cross clamp, after aortic cross clamp and immediately before aortic declamping. Also we selected our patients who have solitary valvular lesion to ensure short time of bypass and cross-clamp, with healthy coronaries to ensure potent delivery of cardioplegic solution however; we found no significant effects regarding lactate release, the use of inotropes, post-operative ICU stay or LVOT VTI
Keywords: Esmolol, cardiac function, cardioplegia, cardiopulmonary bypass, beta-blockade.

Introduction
Many clinical and empirical tests, β-adrenergic preventing factors are developed to be preventive both functionally and structurally in myocardial subjected to ischemia and reperfusion.(7–9) This cardioprotective impact also may be useful through cardiopulmonary bypass (CPB) and cardioplegic arrest. However, the cardiodepressive impacts of these factors

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potentially may extend weaning and causing an insufficient cardiac reply in the postoperative stage. So, particular awareness has been dragged to the ultra-short-acting β-blocker esmolol. From the point of view of protecting the heart, persistent myocardial exudation with high concentrations of esmolol may be helpful in comparsion with potassium-based cardioplegia, to assist agreeable surgical circumstances with slight or no myocardial motion (10–12). Employ of minimize systemic concentrations of esmololperrior, through, or following CPB and cardioplegic arrest in incorporation with mainly employed cardioplegic regimens also have been cleared to be useful, both empirically and clinically.(13–15) In secluded hearts both anoxia and ischemia liberation catecholamine storages, leading to lipolysis and myocardial tissue injury. Esmolol may further decrease the possibility ischemic and re-aspirate injury by preventing the impacts of the endogenous liberation of catecholamines.
When added to refind oxygenated blood cardioplegia, immediately intracoronary transportation of esmolol through the cardioplegic aspirate reveals the myocardium to esmolol with a decresed total systemic dosage. To the authors' knowledge, only 2 investigations have employ esmolol as an additive to cold blood cardioplegia. Refined antegrade, cold, oxygenated, blood cardioplegia is frequently the selected procedure employed to assist cardioplegic arrest and myocardial preventation.16 In this empirical trial, the authors purposed that esmolol as an additive to standard potassium-based blood cardioplegia would enhance the postoperative cardiac function. Cardiac function was evaluated with lactate level in the coronary sinus as a marker after aortic declamping and reperfusion.

Subjects, Materials and Methods

Subjects:

Eighty patients with either sex with solitary valvular disease when listed for non-emergent mitral valve replacement surgery enrolled in this study. This study was performed in the Teaching Hospitals of Cairo University, cardiothoracic surgery theatre from 9/2018 to 1/2019.Then they divided into two groups, group A (Esmolol) 40 patients and group B(control) 40 patients .Their age ranged from 20-50 years with mean equal to 39.5 years for Esmolol group and 37.5 years old for control group .

Exclusion criteria:

Our study excluded any candidate having Myocardial infarction within 2 weeks ,history of reaction or toxicity to esmolol or other beta blockers, New York Heart Association class IV congestive heart failure in spite of treatment, permanent hypotension (systolic blood pressure <80 mm Hg), diseases other than one valve disease , severe pulmonary hypertension, Ejection fraction less than 45%,Patients with coronary artery disease, Patients with congenital heart disease, Patients with previous cardiac surgery, Patients with liver disease, Patients with second or third degree heart block, Patients having resting heart rate less than 50 ppm or Patients using calcium channel blockers.
The study was approved by the ethical committee. All patients were subjected to the following evaluation protocols:

Preoperative evaluation:

Whole normal estimations will be achieved involving CBC, Coagulation pattern, liver function tests, kidney function tests, blood grouping, ECG, Chest X-ray, newly echocardiography ,CK , CK-mb , troponine, lactate and cardiac angiography when appropriate.

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Anesthetic technique:
Premedication:
Morphine sulphate 0.1 mg /kg intramuscular 1 hour before operation.
Midazolam 0.01 to 0.05 mg/kg intravenous in the premedication room.

Induction of anesthesia:
Pancuronium 0.15 mg/kg will be managed to assist endotracheal intubation and refined intraoperative as desired to preserve muscle relaxation. Anesthesia will be preserved employed isoflurane 0.3%–1.5% in oxygen-air mixture (70% oxygen). A central venous line will be incorporated and arterial line for CVP && invasive blood pressure controlling respectively

A 7.5-MHz multiplane TEE probe and system (Vivid 3, GE Medical Systems, Milwaukee, Wis) will be employed for all echocardiographic records. Whole clients will subjected a complete transesophageal echocardiography investigation (TEE) Regarding to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) recommendations. TEE will be used to assess the contractility by estimating the left ventricular ejection fraction

Monitoring and parameters to be measured:
- 5 leads ECG with arrhythmia detector and alarm and with ST segment analysis.
- Invasive blood pressure.
- Central venous pressure.
- Pulse oximetry.
- End-tidal capnography.
- Nasopharyngeal temperature.
- Serial arterial blood gases and electrolytes.
- TEE: according to adapted Simson's rule technique, left ventricular end-diastolic and end-systolic volumes will be studied and the left ventricular ejection fraction (LVEF) will be obtained.
- Serial coronary sinus lactate level.

Interventions:
Each of group (A) patients will receive from esmolol 250 mg/ml 1.5 ml added to one liter of potassium blood cardioplegia 4:1 after cross calmping to be repeated every 25 minutes with every cardioplegia dose.
Each of group (B) will receive potassium blood cardioplegia 4:1 after cross calmping to be repeated every 25 minutes.

Surgical technique:
In whole clients, a median sternotomy will be carried out. CPB will be started following standard aorta-bicavalcannulation, after full heparinization by 300 U/kg heparin sulfate, to reach activated clotting time (ACT) > 480 seconds (23). A membrane oxygenator (Minimax Plus; Medtronic Inc., Anaheim, CA) and a nonpulsatile roller pump (model 10.10.00; Stôckert Instruments; Munich, Germany) will be employed. Venting of the left heart will be carried out with a left atrial vent incorporated during a small opening at the interatrialseptum,retrogradecardioplegia cannula will be incorporated in the coronary sinus during the right atrium . Priming fluids composed of lactated Ringer's solution accomplished with heparin.

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Mild hypothermia (26°C to 28°C) will be employed through CPB. Cold potassium cardioplegia (blood to crystalloid 4:1) with 30 mEq/L of potassium (15 mL/kg for induction), Sodium bicarbonate 13mEq/L will be inoculated into the aortic root following aortic cross clamping. This will be followed by 10 mL/kg every 25 minutes through the antegrade cardioplegia cannula during aortic cross-clamping, and throughout this period, topical myocardial cooling will be used.

Termination of operation:
After termination of cardiopulmonary bypass (CPB), heparin will be antagonized by protamine in both groups. Hemoglobin concentration will be kept above 7gm/dl during CPB and above 9 gm/dl after CPB. All the patients will be transferred to the cardiothoracic intensive care unit (ICU), ECG and arterial blood gases will be done daily.

Statistical Analysis:
Results will be statistically discussed in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate.

Comparison of numerical variables between the study groups will be achieved employing Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. For comparing categorical results, Chi-square ($\chi 2$) test will be carried out. Exact test will be used instead when the expected frequency is less than 5. Relation between different variables will be done using Pearson moment correlation equation for linear correlation in normally distributed variables and Spearman rank correlation equation for non-normal variables with graphic representation using linear regression graph. A probability value (p value) less than 0.05 is believed statistically significant. All statistical calculations will be done employing computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and IBM SPSS (IBM Inc., USA) version 23 for Microsoft Windows.

Results
Eighty patients suffered from isolated mitral valve disease involved in the study. mean age for esmolol group was 39.5 with 42.5 % were males and 57.5 % were females while that of the control group mean age was 37.58 35% were males and 65.5% were females.

Table (1): Perioperative characteristic of patients in the two study groups (Data are presented as mean±SD, numbers, and percentage)

	Esmolol mean/Count	**SD/%**	**Control mean/Count**	**SD/%**	**P value**
age	39.5	7.669	37.58	8.482	0.297
weight	76.00	18.193	77.15	11.762	0.738
height	164.05	17.047	168.78	8.607	0.123
male	17	42.5 %	14	35.0%	0.491
female	23	57.5 %	26	65.5%	

All candidates divided into two groups Group A Esmolol group (40 patients) and group B control group (40 patients)

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Results of Blood pressure before and after bypass on both groups:
Regarding hemodynamics before bypass, esmolol group showed that mean systolic blood pressure was 130.75 ± 25.358 and mean diastolic pressure 76.75 ± 10.952 while that for the control group mean systolic pressure was 133.63 ± 17.722 and mean diastolic pressure was 77.25 ± 10.857

Regarding hemodynamics after weaning from bypass, esmolol group showed that mean systolic pressure was 125.63± 14.683 and mean diastolic pressure was 75.38 ± 10.524 while that for the control group, mean systolic pressure was 123.63 ± 11.356 and mean diastolic pressure was 73.43 ± 11.356. (Table 2).

Table (2): Blood pressure in the two study groups before and after bypass

	Esmolol		**Control**		**P value**
	Mean	**SD**	**Mean**	**SD**	
BP systole before	130.75	25.358	133.63	17.722	0.559
BP diastole before	76.75	10.952	77.25	10.857	0.838
BP systole after	125.63	14.683	123.63	11.356	0.501
BP diastole after	75.38	10.524	73.43	11.356	0.428

Results of ECG before and after bypass
Regarding ECG before bypass, esmolo group showed that 37.5% was normal sinus rhythm (NSR) and 62.5% was atrial fibrillation (AF) while control group was 42.5% was NSR and 57.5% was AF. After bypass, esmolol group showed that 32.5% was NSR, 57.5% was AF, 10% was nodal rhythm and 17.5% needed pacemaker while control group showed that 32.5% was NSR, 60% was AF, 7.5% was nodal rhythm and 20% needed pacemaker.

Table (3): ECG before and after bypass

		Esmolol		**Control**		**P value**
		Count	**%**	**Count**	**%**	
ECG	NSR	15	37.5%	17	42.5%	0.648
before	AF	25	62.5%	23	57.5%	
	Nodal	0	0	0	0	
ECG after	NSR	13	32.5%	13	32.5%	0.921
	AF	23	57.5%	24	60.0%	
	Nodal	4	10.0%	3	7.5%	
Pace	Yes	7	17.5	8	20.0%	0.775
maker	NO	33	82.5%	32	81.3%	

Results of Pre-operative diagnosis
Regarding pre-operative diagnosis, esmolol group 50% had mitral stenosis (MS), 25% had mitral regurgitation (MR), 15% had aortic stenosis (AS) and 10% had aortic regurgitation (AR).

Control group 42.5% had MS, 30% had MR 20% had AS and 7.5% had AR.

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Table (4): Pre-operative diagnosis

		Esmolol		Control		P value
		Count	%	Count	%	
Diagnosis	MS	20	50	17	42.5	0.612
	MR	10	25	12	30.0	
	AS	6	15	8	20.0	
	AR	4	10.0	3	7.5	

Results of CBP and ischemic time

Regarding cardiopulmonary bypass (CPB) time and ischemic time, **esmolol group** showed mean bypass time 89.13± 14.046 and mean ischemic time was 69.28± 13.361.While **control group** mean bypass time was 87.38± 11.8 and ischemic time was 61.95 with ischemic time 61.95± 9.8.

Table (5): CBP and ischemic time

	Esmolol		Control		P value
	Mean	SD	Mean	SD	
CPB time	89.13	14.046	87.38	11.8	0.87
ischemic time	69.28	13.361	61.95	9.8	0.24

Results of Lactate levels before and after clamping and before declamping the aorta.

Regarding lactate withdrawn from the coronary sinus was as follow .For esmolol group, mean lactate level before clamping the aorta was 0.72± 0.27 for control group was 0.74 ±0.169. Mean lactate level after clampimg the aorta for esmolol group was 0.99 ±0.319 which was 0.88 ± 0.187 for the control group. Mean lactate level before declamping the aorta for esmolol group was 1.44± 0.495 which was 1.42± 0.531 for control group.

Table (6): Lactate levels before and after clamping and before declamping the aorta.

	Esmolol		Control		P value
	Mean	SD	Mean	SD	
lactate before	0.72	0.270	0.74	0.169	0.670
lactate after clamp	0.99	0.319	0.88	0.187	0.050
lactate before declamp	1.44	0.495	1.42	0.531	0.818

Result of the use of inotropes and post-operative ICU stay

Regarding the use of inotopes in esmolol group 50% needed dobutamine, 5% needed adrenaline, 4% needed noradrenaline and 35% needed no support at all with mean stay at ICU for 2.33 days ± 0.577 as for control group 52.5% needed dobutamine, 12.5% needed adrenaline, 7.5% needed noradrenaline and 27.5% needed no support with mean stay at ICU for 2.43 days ± 0.675.

Table (7): The use of inotropes and post-operative ICU stay

		Esmolol		Control		P value
		mean/Count	SD/%	mean/Count	SD/%	
Inotropes	None	14	35	11	27.5	
	Dobutamine	20	50	21	52.5	

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	Adrenaline	2	5	5	12.5	
	noradrenaline	4	10	3	7.5	
ICU stay		2.33	0.577	2.43	0.675	0.518

Results of LVOT VTI pre and post bypass

Regarding LVOT velocity time integral VTI we found that esmolol group before bypass had mean VTI was 21.1 ±1.3 while that for control group was 21.8 ±1.1 with p value 0.75

After bypass VTI for esmolol group was 19.1 ±1.2 while for control group was 18.8 ± 0.9 with p value 0.67

Table (8): LVOT VTI pre and post bypass

	Esmolol		**Control**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Before bypass	21.1	1.3	21.8	1.1	0.75
After bypass	19.1	1.2	18.8	0.9	0.67

Discussion

Our study was conducted in Cairo university hospital, cardiothoracic theatre in about 18 months. In our study, we tried to get the benefits of diastolic arrest of potassium cardioplegia and decreasing oxygen consumption properties of esmolol. Also we selected our patients who have solitary valvular lesion to ensure short time of bypass and cross-clamp, with healthy coronaries to ensure potent delivery of cardioplegic solution. By using lactate in the coronary sinus as our primary outcome and ICU stay, inotropes, use of pacemaker and LVOT VTI as secondary outcomes, we found no significant effects regarding using esmolol as a component of cardioplegic solution.

In 2002, Bessho et al (16), in their study; Myocardial preservation with oxygenated esmolol cardioplegia through extended normothermic ischemia in the rat, suggested that Esmolol cardioplegia this may supply on effective sustitute to hyperkalemia. Also In 2013, Fujii M and chambers DJ (17), used esmolol solution on rats compared to hyperkalemic solution, on six different groups, by comparing the recovery of isolated hearts of rats after cardioplegia, they found that Blood-based esmolol cardioplegia enhanced cardioprotective performance compared with hyperkalaemiccardioplegia. They recommended that esmolol-based cardioplegic solution may be a useful substitute to hyperkalaemic solutions.

In both studies we cannot ensure that the hearts of group of esmolol only cardioplegia were arrested in diastole, but it showed higher efficacy during prolonged ischemia.

On the other hand, in 1999 Kuhn-Regnier et al (18) founded that, application of the β-blocker technique through normal CABG was related with lightly preferable functional recovery and minimal constitutional myocardial modification as compared with discontinuous cold blood cardioplegia.

Another opinion was reported by the authors determined that myocardial edema was much more with crystalloid cardioplegia than that with enriched blood with esmolol(19).

The findings of Scorcin et al.(20) in their study shows that Esmolol prolongs effective myocardial maintenance in hypertrophied hearts, by decreasing myocardial oxygen metabolism; Also Coronary glucose and lactate transmyocardial tendencies were comparable in both groups, indicating sufficient myocardial exudation in all clients at all times

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Ethical Clearance:
Taken from Research Ethics Committee at Faculty of Medicine

Source of Funding: Self

No Conflict of Interest: None

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