Original Article

Effect of esmolol on myocardial protection in pediatrics congenital heart defects

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Abstract

Background: Although it is accepted that inducing cardioplegia is the gold standard in myocardial protection, there is still no consensus on the exact type of the cardioplegia. There are fewer studies on the type of the cardioplegia in hearts of the children than adults and they are contradictory. The effects of esmolol have been reviewed (a type of ultrashort-acting beta-adrenergic antagonist, i.e., ß-blockers) in conjunction with the cardioplegia due to the effect of the β-blockers in reducing the myocardial ischemia and reperfusion.

Materials and Methods: The left ventricle ejection fraction (LVEF), systolic blood pressure, central venous pressure (CVP), heart rate, etc., were recorded separately in patients who received the cardioplegia without esmolol ($n = 35$) and with esmolol ($n = 30$) and matched for the age and sex.

Results: The amount of inotrope used in the group without esmolol (100%) was considerably higher than in the group with esmolol (86.7%). Postoperative arrhythmias did not differ significantly between the two groups. There was no significant difference in the duration of cardiopulmonary bypass (CPB), time of the extubation, length of the ICU stay, the first day EF after surgery, and the first week EF after surgery as well. Creatinine kinase-MB (CKMB) was significantly higher in the group without esmolol during operation than in the group with esmolol.

Conclusions: The patients who received cardioplegia along with esmolol had less inotropic requirement after operation, and increase in EF and cardiac output (CO) 1 week after surgery. In addition, it reduced damage to the heart during surgery, and patients may have greater stability in the cardiac conduction system.

Key Words: Cardioplegia, esmolol, myocardial protection, pediatrics

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INTRODUCTION

Gibbon described and used a mechanical extracorporeal oxygenator for the first time and termed it the heart-lung machine. He performed the first successful open heart surgery in the world on May 6, 1953, using a heart-lung machine while was repairing an atrial septal defect (ASD). In 1954, Lillehei reported the first effective use of the extracorporeal circulation in repairing congenital heart disease (CHD) using cross-circulation, the patient's parent functioning as the oxygenator. Subsequent attempts to use the heart-lung machine to help correct CHD were met with high morbidity and mortality rates until 1971 (Barratt-Boyes), and 1974 (Castaneda), when hypothermic circulatory arrest was used in an attempt to refine the procedure.

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Myocardial protection protocols include reduced metabolic activity by hypothermia, therapeutic arrest of the myocardial contraction, and all of the electrical activities of the myocardium by administration of the cardioplegic solution (the potential depolarization of the cell membrane by the high potassium dosage of the cardioplegia).[1-3] Both the Laws have been accepted clearly, which reduce energy consumption. Cardiac tolerance to ischemia increases significantly by reducing the energy consumption and thus the oxygen demand. In 1984, Bull *et al*. suggested in a study concerned with the usefulness of cardioplegia in pediatric cardiac surgery[4] that it has been used as the mainstay of myocardial protection in pediatric cardiac surgery from that time. If the results of the cardioplegia are quite clear, why has the usefulness of cardioplegia for the heart been questioned during its evolution? Few studies have been performed approximately in relation to myocardial protection of children, and comparing them is complicated because of lack of the insistence on the pediatrics.

Although it is accepted that inducing cardioplegia is the gold standard in myocardial protection, there is still no consensus on the issue.[5] Studies conducted on this topic of children are fewer than of adults and are contradictory.[6,7] On the one hand, there are specific ways in which children's hearts are different from those of adults; on the other hand, it is difficult to evaluate this issue because of the lack of clinical and laboratory studies.[5] In adults, 90% of adenosine triphosphate (ATP) production is achieved from fatty acid oxidation, and glucose is the main substrate in children's hearts.[5]

Many experiments and clinical studies indicate that β-adrenergic antagonists (β-blockers) can reduce the extent of the myocardial ischemia and reperfusion.[8-11] Although effective mechanisms of these medicines in myocardial ischemia are not completely clear, some possible mechanisms include decreasing heart rate and contractility (by reducing myocardial oxygen consumption),[12] decreasing sympathetic tonicity,[13] changes in myocardial substrate consumption,[14] stability of the cell membranes,[15] and reducing peroxidation of phospholipids of the membrane.[16]

Administration of the β-blockers contributes to myocardial protection during cardiac surgery via hypothermic arrest.[8-11] However, β-blockers are avoided in CPB because they are considered as a negative inotrope and may cause difficulty in terminating CPB.[17] Esmolol is metabolized rapidly by the arylesterase in blood, so its half-life is only 9 min. Thus, the negative inotropic effect of the β-blockers may not be considered if it is only used in association with the cardioplegia and not after that.[18]

MATERIALS AND METHODS

Written consent was obtained during the preoperative interview, after taking approval from the Ethics Committee of Isfahan University of Medical Sciences. The type of the study was a prospective clinical trial. The study population comprised infants and children with CHD: He ASD and ventricular septal defect (VSD) patients who were candidates for open-heart surgery using cardioplegia during the operation. Sixty-five patients for heart surgery including CPB and aortic cross-clamping were chosen randomly and divided into two groups: 1) The esmolol group (30 patients), who received esmolol during the cardioplegia infusion and 2) the control group (35 patients). Data collection was done using a checklist.

Exclusion criteria included: 1) Patients who were not in the age group <18 years, 2) patients who were not candidates for receiving cardioplegia during operation, 3) patients who had significant clinically postoperative residual VSD or ASD, and 4) patients who have the other grounded cardiac disease before surgery. The Chi-square test, Fisher's exact test, the Mann-Whitney U test, the paired *t*-test, the analysis of variance (ANOVA), the independent *t*-test, and repeated observations were used statistically. Data analysis was performed by using the SPSS software (ver. 20).

In this study, a single-dose system was used for the crystalloid cardioplegia solution. St. Thomas' Hospital (STH) is one type of cardioplegic solution that was produced in 1970. It consisted of magnesium chloride, potassium chloride, procainamide hydrochloride, sodium hydroxide, and water. Each vial contained 20 ml of STH solution that should be combined with 1 l of Ringer's serum before injection. Its effective mechanism occurs through a high potassium dose. STH solution inhibits activity of the Na^+-K^+ pump during ischemia, thus limiting the increase in intracellular sodium load due to the ischemia and improving cellular function after ischemia.

For the cardioplegia in the esmolol group, from 250 mg/ml of esmolol 1.5 ml was added to 1 l of STH solution that was prepared on the same day. Cardioplegic solution 10-15 ml/kg in a single dose was injected into the aortic root after aortic clamping and cooling the patient simultaneously.

After induction of the anesthesia, intubation, and taking the arterial line and central venous catheter, the hemodynamic parameters such as systolic arterial blood pressure, central venous pressure (CVP), and heart rate were recorded. Then CKMB checking was done, along with the first arterial blood gas (ABG) sample followed by sternotomy. Next the cannulation of superior vena cava (SVC), inferior vena cava (IVC), and aorta was done. After the establishment of the CPB, the aorta was clamped, the patient was cooled to a temperature of 28°C, and the cardioplegic solution at 4°C was injected into the aortic root. Then ASD and VSD repairing were done. Another CKMB check was done during CPB. After the completion of the surgery, the patient was warmed, aortic clamp was removed and the CPB along with the operation were terminated. The patient was sent to the intensive care unit (ICU), and CKMB along with ABG were done once again. Systolic arterial blood pressure, CVP, heart rate, urine output, serum potassium, checking of the coldness of the extremities, and estimation of the amount of the administration of dopamine and epinephrine were recorded after the first 4 h postsurgery. They were repeated the day after the surgery. Left ventricle ejection fraction (LVEF) and cardiac output (CO) were measured on the first day and 1 week after the surgery and recorded. Finally, time of the extubation, ICU stay, and postoperative complications were recorded.

RESULTS

Mean age, diagnosis, operation duration, and postoperative data are given for each group in Table 1. Sixty-five patients were enrolled in this study. Thirty patients were male and 35 female. Forty of the cases were VSD, 21 were ASD, and four were ASD + VSD. CPB time mean was 72 min (range: 30-123 min) for all the patients, aortic clamp time was 45 min (range: 16-89 min). The means of CPB and clamp times are summarized for each group in Table 1. The weaning from CPB was uneventful in all the patients. Low-dose dopamine administration (up to 5 μg/kg/min) in 21 patients, moderate dose dopamine (between 5 μg/kg/min and 10 μg/kg/min) in 18 patients, high dose dopamine (above 10 μg/kg/min) in 22 patients, and epinephrine (0.05-0.1 μg/kg/min) in four patients were necessary. The administration rates of the inotropic medicines are shown for both the groups in Table 2. The preoperative and postoperative CKMB means were the same in both the groups, but CKMB was significantly different during surgery between the two groups [Table 3]. The serum potassium was higher than 4 meq/l in eight cases of the esmolol group and in four cases of the control group ($P = 0.11$) for the first 4 h after surgery. Coldness of the extremities was observed in four patients of the esmolol group and in two patients of the control group ($P = 0.26$).

Urine output (U/O) (<1 ml/kg/hr) after first 4 h postsurgery, on the first postoperative day ($P = 1$), renal failure, and the use of peritoneal dialysis ($P = 1$) were not significantly different between the two groups. Postoperative arrhythmia ($P = 0.29$), neurological complications, and the other adverse effects ($P = 1$) were not significantly different between the two groups. However, there were two cases of the paroxysmal tachyarrhythmia in the control group. The extubation time mean was 13.9 h in the control group and 17.2 hrs in the esmolol group ($P = 0.33$). The duration of ICU stay mean was 2.27 days in the esmolol group and 2.4 days ($P = 0.59$) in the control group. The comparison between hemodynamic parameters, that is,: Systolic blood pressure, CVP, and heart rate are shown in Table 4 in both the groups.

Table 5 indicates that although the first EF was in the normal range in both the groups, the preoperative EF mean is 71.9 ± 1.3 in the esmolol group and 65.5 ± 1.7 in the control group, that is, they are significantly different ($P = 0.004$). There are significantly different COs on the postoperation day between both the groups, but no significant difference between both the groups in 1 week after surgery. It is necessary to mention that the preoperative CO variable was removed due to insufficient volume of the samples. The comparison of the CO at different times indicated that there was no significant difference ($P = 0.87$) in the control group but was significant in the esmolol

Table 1: Characteristics of patients

Number of patients	Sex	Age (months)	Cardioplegia type	Weight (kg)	Diagnosis	CPB time (min)	Clamp time (min)	Extubation time (h)	ICU stay (day)
8	2M-6F	31 (11-48)	ESMOLOL	11 (8-14)	ASD	48 (36-60)	24 (16-33)	5 (4-7)	1.5 (1-2)
13	4M-9F	21 (7-36)	CONTROL	10 (6-14)	ASD	49 (30-64)	22 (16-36)	6 (3-12)	1.8 (1-2)
20	10M-10F	31(7-120)	ESMOLOL	10 (6-22)	VSD	85 (66-100)	56 (39-66)	19 (4-48)	2.5 (2-3)
20	12M-8F	36(7-120)	CONTROL	10 (4-21)	VSD	79 (61-123)	54 (31-89)	18 (6-50)	2.7 (2-6)
2	2M-0F	7	ESMOLOL	5	ASD and VSD	80	52	48	3
2	0M-2F	9	CONTROL	10	ASD and VSD	98	70	20	3

Table 2: Administration of inotrope

Variable	No esmolol (%)	Esmolol (%)	*P* value
Inotrope administration	35 (100)	26 (86.7)	0.04
No dopamine administration	0 (0.0)	4 (13.3)	
Dopamine <5 μg/kg/min	11 (31.4)	10 (33.3)	0.28
Dopamine 5-10 μg/kg/min	12 (34.3)	6 (20.0)	
Dopamine >10 μg/kg/min	12 (34.3)	10 (33.3)	
Epinephrine administration	0 (0.0)	4 (13.3)	0.04

Table 3: Characteristics of CKMB

Time	Mean±SE		*P* value
	No esmolol	Esmolol	
Preoperative			
CKMB	40.9±3.6	39.7±3.2	0.81
Intraoperative			
CKMB	110.9±10.6	92±6	0.04
Postoperative			
CKMB	135.1±7.7	136.5±6.4	0.89
P value	<0.001	<0.001	

CKMB: Creatinine kinase-MB

Table 4: Characteristics of systolic blood pressure, CVP, and heart rate in both the groups

Time	SBP (mmHg)	CVP (mmHg)	PR (bpm)	*P* value
Preoperative				P_S=0.68
E	81.4±1.8	9.1±0.5	142.1±3.1	P_C=0.43
C	82.6±2.1	8.4±0.6	142.3±2.9	P_R=0.93
First 4 h after surgery				P_S=0.89
E	104.3±2.8	7.4±0.45	141.6±2.8	P_C=0.04
C	104.8±2.5	9.0±0.75	138.7±4.1	P_R=0.57
Postoperative day				P_S=0.04
E	100.3±1.9	8.1±0.7	124.9±2.1	P_C=0.07
C	108.7±3.3	9.5±0.6	127.6±3.9	P_R=0.56

SBP: Systolic blood pressure, CVP: Central venous pressure, PR: Pulse rate, E: Esmolol group, C: Control group, P_S: *P* value of SBP, P_C: *P* value of CVP, P_R: *P* value of PR

Table 5: Characteristics of EF

Time	Mean±SE		*P* value
	No esmolol	Esmolol	
Preoperative			
EF	71.9±1.3	65.5±1.7	0.004
CO			
Postoperative day			
EF	65.3±1.3	64.2±1.1	0.52
CO	1874±66	1662±58	0.007
A week after surgery			
EF	67.9±0.9	69.1±1.3	0.47
CO	1864±90	1871±116	0.96
P value			
EF	0.001	0.01	
CO	0.87	0.03	

EF: Ejection fraction, CO: cardiac output

group ($P = 0.03$). The systolic blood pressure mean on the postoperation day in the esmolol group was 108.7 and 100.3 in the control group that were significantly different ($P = 0.04$). There were significant differences in mean CVP for the first 4 h after surgery and on the first day after surgery in the two groups. There were no significant differences in pulse rates before surgery, 4 h after surgery, and on the first day after surgery in the two groups.

DISCUSSION

It is necessary to mention that significant differences did not exist in age, sex, weight, and type of the disease in both the cases and the control group, so these contributed to a more accurate analysis of the findings. Although the need to use inotrope in the esmolol group was less than in the control group, the need to use a stronger inotrope (epinephrine) was higher in those that needed inotrope (because of the significantly lower EF in the esmolol group). There were no significant differences between the two groups in the indices of the serum K^+ 4 meq/l after the first 4 h postsurgery, coldness of the extremities, and the urine output was less than 1 ml/kg/h after the first 4 h postsurgery and the day after, which indicates cardiac function. This issue rejected the negative inotropic effect of esmolol as a β-blocker. Aortic clamp time and CPB were not statistically significant in the two groups. This indicates that esmolol at least does not possess negative inotropic effects that attributed to the other ß-blockers.

Cork *et al*. proposed the use of the esmolol can cause prolonged CPB and higher postoperative serum potassium level in 1995, but as you observed it is contrary to my study results.[17] In addition, this study's results are contrary to the study by Chambers *et al*. that proposed that cardioplegia along with deoxygenated esmolol can cause weaker myocardial protection in 2002.[18]

Although postoperative complications did not differ significantly in the two groups, two cases of arrhythmia were observed in the control group, which were not observed in the esmolol group. Heart block and bradycardia were not observed in the esmolol group compared with the control group. Although preoperative EF in the cardioplegia group along with esmolol was significantly lower than the esmolol group (at first both were in the normal range), it increased significantly 1 week after surgery (EF reduced significantly in the nonesmolol group, namely, the EF in the nonesmolol group was significantly lower than in the control group 1 day after surgery and 1 week after surgery). Although CO in the esmolol group was significantly lower than in the control group on the postoperation day, it increased significantly in the esmolol group and

reached to the level of the control group 1 week after surgery. Unfortunately, it is not clear that lower CO in the esmolol group on the postoperation day is due to the negative inotropic effect of the esmolol group or preoperative CO may be considerably lower in the esmolol group (preoperative EF was significantly lower in the esmolol group). Unfortunately, the comparison of the preoperative CO was excluded due to the lack of the samples, although it could be helpful.

Blood pressure variation

Blood pressure (BP) increased significantly in both the groups after surgery in comparison with before the surgery, may be due to the correction of the grounding disease. BP in the nonesmolol cardioplegia group was significantly higher than in the esmolol cardioplegia group 1 week after surgery. It is clear that the increase in BP can cause too much burden on the heart and has a negative effect on its activity.

Central venous pressure variation

Significant difference was observed between the case and the control group after the first 4 h postsurgery and 1 day after that. Lower CVP in the esmolol group indicated better heart functioning. Bradycardia and heart block were not observed in the esmolol group because of its β-blocker side effects. Although there were no significant differences between the nonesmolol group and the esmolol group in the two cases of arrhythmia, it may be concluded that esmolol can cause more heart stability.

The comparison of CKMB shows that esmolol can prevent the rapid rise in CKMB during surgery: In other words, it can cause more myocardial stability and reduce the velocity of the myocardial damage. Ultimately, in this study, it did not reduce the extent of the damage to the heart myocardium caused by the CPB and inflammatory cells.

Finally, time of the extubation and the duration of ICU stay did not significantly differ between the two groups. Results of the extubation time and the ICU stay were the same as in the study of Borowski *et al*. was in 1998.[19]

CONCLUSIONS

Esmolol cardioplegia reduces inotrope requirement after surgery, increases LVEF 1 week after surgery, decreases heart injury during surgery, and may cause more cardiac conduction system stability. Nevertheless, esmolol does not affect the extubation time and the ICU stay. It seems that esmolol is appropriate in the low EF selected patients.

Finally nowadays, it is important to have high-quality surgery, lower mortality, lower extubation time, and ICU stay. Even an ideal cardioplegia is not so strong that it can achieve these goals if the other factors are not at the same level. However, the following points are recommended:

- Despite the fact that the mean CPB time was 69 min in this study, the effect of esmolol should be investigated in pediatric cardiac surgery to find whether CPB time is greater than 60 min
- The effect of esmolol should be assessed in patients with EF less than 50% who are candidates for pediatric cardiac surgery, irrespective of the grounding disease
- Finally, comparing esmolol with the single-dose crystalloid cardioplegia versus esmolol with multidose blood cardioplegia is recommended in terms of the myocardial stability and the rate of reduction in EF after surgery.

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