Turk Gogus Kalp Dama 2016;24(4):627-632
doi: 10.5606/tgkdc.dergisi.2016.13082

The effect of esmolol on myocardial protection in patients with tetrology of Fallot

Fallot tetralojili olguların miyokardiyal korunmasında esmololün etkisi

Füsun Güzelmeriç,[1] Ömer Faruk Şavluk,[1] Yasemin Yavuz,[1] Eylem Tunçer,[2] Hakan Ceyran,[2] Alican Hatemi[2]

Departments of [1]Anaesthesiology and Reanimation, [2]Pediatric Cardiac Surgery,
Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Background: In this article, we examined the effects of intraoperative esmolol infusion on myocardial protection in children operated on for tetralogy of Fallot.

Methods: The study involved 50 pediatric patients (29 boys, 21 girls; mean age 12.6±2 months; range 9 to 20 months) operated on for tetralogy of Fallot between January 2014 and November 2015. We randomly divided the children into two groups and started esmolol infusion as an intraoperative agent for one group (study group), and with normal saline infusion for the other (control group). We started the esmolol infusion with the induction of anesthesia (0.05 mg/kg/min) and, then, reduced the dose by half (0.025 mg/kg) during the cardiopulmonary bypass. We took blood samples for creatine kinase-MB, troponin I, and lactate 10 minutes after the tracheal intubation, five minutes before the cardiopulmonary bypass, five minutes after the cardiopulmonary bypass, at the end of the surgery, at the four hours postoperatively, and on the first postoperative day. We recorded the hemodynamic parameters.

Results: The levels of creatine kinase-MB, troponin I and lactate were found to be significantly higher in the control group than the study group ($p<0.05$). The mean arterial pressures did not differ between the groups; however, we found that the heart rate in the study group was significantly lower than the control group ($p<0.05$). We found lower inotropic scores in the study group ($p<0.05$).

Conclusion: In pediatric cardiac surgery, the use of intraoperative esmolol may be effective in protecting from myocardium damage. Using an intraoperative esmolol infusion including the cardiopulmonary bypass in children is safe and reduces the postoperative inotropic score.

Keywords: Cardiopulmonary bypass; esmolol; pediatric anesthesia.

ÖZ

Amaç: Bu çalışmada, Fallot tetralojisi nedeniyle ameliyat edilen çocuklarda ameliyat sırası esmolol infüzyonunun miyokardın korunması üzerine olan etkileri araştırıldı.

Çalışma planı: Ocak 2014 - Kasım 2015 tarihleri arasında Fallot tetralojisi nedeniyle ameliyat edilen 50 çocuk hasta (29 erkek, 21 kız; ort. yaş 12.6±2 ay; dağılım 9-20 ay) çalışmaya dahil edildi. Çocuklar rastgele iki gruba ayrıldı ve gruplardan birine ameliyat sırasında esmolol infüzyonu (çalışma grubu) ve diğer gruba serum fizyolojik infüzyonu (kontrol grubu) başlandı. Esmolol infüzyonuna anestezi indüksiyonu ile başlandı (0.05 mg/kg/dk.) ve ardından kardiyopulmoner baypas sırasında doz yarıya indirildi (0.025 mg/kg). Kreatin kinaz-MB, troponin I ve laktat için kan örnekleri trakeal entübasyondan 10 dk. sonra, kardiyopulmoner baypastan beş dk. önce, kardiyopulmoner baypastan beş dk. sonra, ameliyat sonunda, ameliyat sonrasında dördüncü saatte ve ameliyat sonrası birinci günde alındı. Hemodinamik parametreler kaydedildi.

Bulgular: Kreatin kinaz-MB, troponin I ve laktat düzeyleri kontrol grubunda, çalışma grubundan anlamlı olarak yüksek bulundu ($p<0.05$). Gruplar arasında ortalama arter basınçları farklılık göstermedi; ancak, kalp hızı çalışma grubunda kontrol grubundan anlamlı olarak düşük bulundu ($p<0.05$). Çalışma grubunda inotrop skoru daha düşük bulundu ($p<0.05$).

Sonuç: Pediyatrik kalp cerrahisinde ameliyat sırası esmolol kullanımı miyokardı hasardan korumada etkin olabilir. Kardiyopulmoner baypası da kapsayacak şekilde çocuklarda ameliyat sırası esmolol infüzyonu kullanımı güvenlidir ve ameliyat sonrası inotrop skorunu azaltmaktadır.

Anahtar sözcükler: Kardiyopulmoner baypas; esmolol; pediyatrik anestezi.

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2016.13082
QR (Quick Response) Code

Received: February 02, 2016 *Accepted:* April 13, 2016

Correspondence: Füsun Güzelmeriç, MD. Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Anestezi ve Reanimasyon Kliniği, 34865 Cevizli, Kartal, İstanbul, Turkey.
Tel: +90 216 - 500 15 00 / 1455 e-mail: fusunguzelmeric@gmail.com

Open heart surgery on cardiopulmonary bypass (CPB) may be associated with myocardial injury.[1] Although immature myocardium is more tolerant to ischemia than adult myocardium, myocardial injury and mortality rate are higher in the younger age group following cardiac surgery with ischemic arrest.[1] Risk factors of myocardial injury are associated with the immaturity of the myocardium, the anatomical or physiological impact of the various congenital heart defects, and surgical procedures.[1]

Acute hypoxia and cyanosis are common physiological stresses in children with congenital heart disease.[1] Prolonged hypoxia reduces the antioxidant reserve capacity with reduced endogenous superoxide dismutase, catalase, and glutathione. Chronic hypoxia also depletes adenosine triphosphate (ATP) and glycogen stores and predisposes the myocardium to a significant injury.[1] Children with cyanotic congenital heart disease undergoing corrective cardiac surgery are more susceptible to myocardial re-oxygenation/reperfusion injury than acyanotic patients.[2] It is considered that hypoxia in cyanotic children reduces the antioxidant reserve capacity, leading to oxidative stress of ischemia.[2] Children with obstructive right- or left-sided lesions and those with increased vascular resistance have also ventricular hypertrophy.[3] Depletion of high-energy phosphate stores and increased myocardial oxygen demand with hypertrophy intensify ischemic risk. Total correctional operations of tetralogy of Fallot (TOF) include atrial, ventricular, and intracardiac myocardial incisions and excisions. As these manipulations exacerbate the risks of myocardial injury, myocardial protection is more important in these patient groups.[3]

Using beta-adrenergic receptor antagonists in adult cardiac surgery is one of the treatment options for myocardial protection.[4,5] However, since cardiac output relies on heart rate for pediatric patients, the use of such medication is restricted. Esmolol, a beta-1 adrenoceptor blocker which is rapidly metabolized by the arylesterase in the blood, has an extremely short duration of action.[6,7] Esmolol reduces not only the heart rate and myocardial contractility, but also myocardial oxygen demand.[8] This technique may cause difficulty in weaning from CPB in adult cardiac surgery due to its negative inotropic effects.[8] Although its use as a cardioprotective agent is pervasive, it is rarely used in pediatric cardiac surgery thanks to its protective ability against the ischemic damage.

As in adult cardiac surgery, troponin I, and creatine kinase-MB (CK-MB) are used as indicators of myocardial damage in pediatric cardiac surgery. We examined the effects of intraoperative esmolol infusion on myocardial protection in children operated on for TOF.

PATIENTS AND METHODS

This randomized research study was carried out with the enrollment of 50 children (29 boys, 21 girls; mean age 12.6±2 months; range 9 to 20 months) whose TOF was repaired between January 2014 and November 2015. A written informed consent was obtained from each parent or legal guardians of the patient. The study protocol was approved by the institutional ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We randomly divided the patients into two groups: one with esmolol infusion (study group) and one with normal saline infusion (control group). We excluded patients with renal or hepatic impairment and those who had a history of asthma or allergy.

After the patients were pre-medicated with intramuscular ketamine of 5 mg/kg and atropine of 0.01 mg and monitored by electrocardiography (five-lead), pulse oximeter and cerebral oximeter, peripheral venous and radial artery cannulations were performed. The anesthetic induction was performed with fentanyl (5 μg/kg), midazolam (0.1 mg/kg) and rocuronium bromide (1 mg/kg). After the tracheal intubation, mechanical ventilation was initiated in the pressure-controlled mode, the pressure levels were adjusted to obtain a suitable tidal volume and normal arterial CO_2 pressure. Anesthesia continuation was maintained with intermittent dosing of midazolam (0.05 mg/kg) and rocuronium bromide (0.6 mg/kg) and of fentanyl infusion (5 μg/kg/hr).

Esmolol infusion was started in the form of continuous infusion (0.05 mg/kg/min) through the peripheral vein together with anesthetic induction and, then, given by reducing the dosage by half during the CPB (0.025 mg/kg) and maintained until the end of surgery. The heart rate (HR) and mean arterial pressure (MAP) were recorded 10 minute phases following the tracheal intubation, five minutes before the CPB, five minutes after the completion of the CPB, and at the end of the surgery. Cardiopulmonary bypass, aortic cross-clamp time, and the vasoactive inotropic score (VIS) were also recorded (VIS= dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose + 10 x milrinone dose (μg/kg/min) + 10.000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min).[9]

Blood samples for CK-MB and cardiac troponin I were taken after induction before of CPB, after CPB, after surgery in the pediatric intensive care unit (ICU), and postoperative first day. Each sample was evaluated immediately.

All patients received 3 mg/kg heparin before cannulation for CPB. Activated coagulation time was maintained over 400 seconds. Crystalloids and erythrocyte suspensions were used for prime solutions and hematocrit levels were maintained at 25 to 30%. Non-pulsatile CPB flow was used and MAPs were maintained at 40 to 50 mmHg. Mild hypothermia (28-30 °C) was performed during the CPB. For myocardial protection, cold (4 °C) blood cardioplegia was used for 20 minutes intermittently. The patients were slowly re-warmed after the closure of the ventricular septal defect (VSD) and reconstruction of the right ventricular outflow and removal of the aortic clamp. Before the initiation of weaning from the CPB, optimal conditions both in hemodynamic parameters and blood gas management were achieved.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 19.0 software (IBM Corporation, Armonk, NY, USA). Data were expressed in mean ± SD. Categorical variables were analyzed using the chi-square test. Normally distributed data were analyzed using the two-tailed Student's test. Repeated measurements were analyzed using one- and two-way analysis of variance (ANOVA). A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 50 patients whose TOF was repaired through CBP were included. Demographic characteristics of the patients are shown in Table 1. There was no difference in the age, gender, and weight of the patients.

Table 1. Demographic characteristics of patients

Patient characteristics	Control group (n=25)		Study group (n=25)	
	n	Mean±SD	n	Mean±SD
Age (month)		12.7±1.8		13±2.1
Gender				
Female	10		11	
Male	15		14	
Weight (kg)		10±0.8		10.6±1.7
McGoon ratio		1.4±0.3		1.4±0.2

SD: Standard deviation.

Hemodynamic parameters are presented in Table 2. The heart rate was significantly lower in the study group after induction, before of CPB, after CBP, and at the end of surgery (p<0.05). The MAP was also lower in study group after induction, before of CPB, after CBP and at the end of surgery; however, it did not reach statistical significance.

There was no significant difference in the duration of aortic cross-clamp and number of patients with spontaneous heartbeats between the two groups (p>0.05). We found the inotropic score in the study group to be significantly lower than the control group (12.65±3.75 in control group vs 9.36±4.35 in study group) (p<0.05) (Table 3).

Plasma CK-MB and troponin I values are shown in Tables 4 and 5. In both groups, plasma CK-MB and troponin I values after CPB, after surgery in pediatric ICU, and on the first postoperative day were significantly higher than the induction phase (p<0.05). Plasma CK-MB and troponin I values after CPB, after surgery in pediatric ICU, and on the first postoperative day in the study group were significantly lower than the control group (p<0.05).

DISCUSSION

Our study included children whose TOF was repaired through CBP. We found that continuous intraoperative

Table 2. Intraoperative hemodynamic parameters

	Control group		Study group	
	Heart rate	MAP	Heart rate	MAP
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Induction	138±16	74±8	136±20	73±6
Before cardiopulmonary bypass	132±10	66±6	127±14*	64±4
After cardiopulmonary bypass	148±18	67±5	134±16*	65±8
End of surgery	141±19	62±6	130±12*	60±5

MAP: Mean arterial pressure (mmHg); SD: Standard deviation; * p< 0.05.

Table 3. Surgical data

Time (in minutes)	Control group	Study group
	Mean±SD	Mean±SD
CPB time	109.3±6.9	111.1±19.5
Cross-clamp time	76±2.2	73.6±10.4
Operation time	201.4±8.2	201.1±18.6

SD: Standard deviation; CPB: Cardiopulmonary bypass; * p<0.05.

esmolol infusion reduced plasma levels of CK-MB and troponin I. Esmolol significantly reduced the heart rates and the inotrope scores, but had non-significant effect on the MAP.

To date, multiple markers have been used to detect perioperative myocardial injury and to evaluate the efficacy of various preservation strategies.[1] The most widely used biochemical markers are the plasma levels of CK-MB and troponin I, which are secreted by damaged myocardium.[1] The level of intracellular Ca^{++} increases with ischemia and reperfusion and the cell's membrane is broken down and cell contents are released to the extracellular matrix.[1] Increasing levels of blood CK-MB after the myocardial damage is an indicator of cell rupture and membrane damage.[1] The level of plasma troponin I is used as an indicator of reperfusion damage, as well.[10] Troponin levels have been found to be correlated with postoperative deaths occurring after CPBs.[11] Cardiac troponin I has shown correlation with the score which demonstrates the seriousness of cardiac surgery in children.[12,13] Correlation between the levels of plasma troponin I higher than 100 µg/L after CPB in children and postoperative mortality has been put forward.[12-14] In pediatric cardiac surgery, surgical interventions may require ventricular incision and myocardial resection, which increases postoperative CK-MB and troponin I levels. Therefore, obtaining samples for myocardial damage indicators during similar operations is important to provide homogeneity. In our study, the levels of plasma CK-MB and troponin I in the blood samples taken after CPB were found to be significantly higher compared to baseline values. In the study group, the plasma CK-MB and troponin I values after the CPB period, in the fourth postoperative hour, and first postoperative day were significantly lower compared to the controls (p<0.05).

Although both heart rate and MAP decreased after esmolol infusion, the decrease of MAP levels was non-significant. Our results may suggest that the esmolol dosage used in our study is so optimal that it can reduce the heart rate without affecting the MAP significantly. After repair of TOF, a low cardiac output state may develop as a result of right ventricular diastolic failure; this most likely results from the exposure of the hypertrophied right ventricle to CPB and reperfusion injury. As the systolic function is intact in these cases, inotropic agents have little benefits.[3] Esmolol may

Table 4. Plasma levels of creatine kinase-MB

Creatine kinase-MB	Control group	Study group	
	Mean±SD	Mean±SD	
Induction	21.1±4.2	21.7±4.8	0.59
Before cardiopulmonary bypass	21.1±3.4	21.9±2.3	0.61
After cardiopulmonary bypass	181.2±50.8	131.8±59.5*	<0.05
After surgery in pediatric ICU	203.2±42.5	120.3±37.6*	<0.05
Postoperative first day	81.5±6.0	69.8±7.74*	<0.05

ICU: Intensive care unit; SD: Standard deviation; * p<0.05.

Table 5. Plasma levels of troponin I

Troponin I	Control group	Study group	
	Mean±SD	Mean±SD	
Induction	0.7±0.7	0.6±0.5	0.64
Before cardiopulmonary bypass	0.7±0.5	0.6±0.7	0.61
After cardiopulmonary bypass	59.5±3.4	48.7±4.3*	<0.05
After surgery in intensive care unit	63.2±2.3	50.3±3.2*	<0.05
Postoperative first day	41.9±3.5	29.9±3.6*	<0.005

SD: Standard deviation; * p<0.05.

improve the diastolic dysfunction of the right ventricle by decreasing the myocardial oxygen consumption which can be invaluable factor for the myocardial protection.

Since cardiac output is more dependent on the heart rate in children than in adults, maintaining heart rate is critical in this patient population. In terms of the infusion dose of esmolol for children, a dose of 0.025 to 0.2 mg/kg/min is well-tolerated for infants, while the dose for children between 2 and 16 years of age is 1 mg/kg/min.[15] In one of the studies in which esmolol infusion was used for children operated on for the treatment of VSD, a dose of 0.05 mg/kg/min was used until the CPB, 0.03 mg/kg/min during the bypass and 0.03-0.05 mg/kg/min after CPB.[16] In our clinical practice, we have been using esmolol infusion and, since we have experienced that doses higher than 0.07 mg/kg/min may negatively affect the hemodynamic parameters, we have fixed the dose at 0.05 mg/kg/min. During CPB, the dose is reduced to 0.025 mg/kg/min. In general, β-adrenergic blockers are avoided in CPB, as they are considered negative inotropes and may cause difficulty in terminating CPB.[7] However, as esmolol is metabolized rapidly by the arylesterase in human blood, its half-life is only nine minutes. Therefore, their usage during CPB seems safer than other β-adrenergic blockers.[6,7]

Beta-adrenergic blockers may demonstrate a protective effect against myocardial ischemia by decreasing the consumption of oxygen and adenosine triphosphate in myocardial metabolism.[17,18] Besides, it is known that beta-blockers establish a balance between the need for and provision of oxygen by increasing the blood flow into the ischemic region.[19] Beta-blockers also reduce the systemic lactate production.[20] This effect is associated not only with the reduction of lactate production, but also with increasing lactate clearance secondarily to the recuperation of blood flow in the liver.[20] In our study, lactate levels in both groups increased after CPB, but returned to baseline levels on the first postoperative day. The blood lactate levels in the study group were found to be significantly lower than the control group ($p<0.05$).

Hypercyanotic spells affect the anesthetic approach in TOF.[21] Increasing levels of blood catecholamine during anesthesia causes the occurrence of those spells. By repressing catecholamine levels in this group of patients, esmolol will prevent intraoperative hypoxic attacks. No intraoperative cyanotic attack was observed in the study group. A hypercyanotic spell was observed in one patient in the control group which was corrected by increasing the depth of anesthesia and fluid management.

In conclusion, our study results showed that in children whose tetralogy of Fallot was repaired using cardiopulmonary bypass, esmolol infusion reduced postoperative plasma levels of creatine kinase-MB, troponin I, and lactate levels. Therefore, esmolol infusion, besides reducing the heart rate during pediatric cardiac surgery when well-titrated, does not likely to cause a significant reduction in the mean arterial pressure.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Mossad EB, Farid I. Vital organ preservation during surgery for congenital heart disease. In: Lake CL, Booker PD, editors. Pediatric cardiac anesthesia. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 266-90.
2. Modi P, Imura H, Caputo M, Pawade A, Parry A, Angelini GD, et al. Cardiopulmonary bypass-induced myocardial reoxygenation injury in pediatric patients with cyanosis. J Thorac Cardiovasc Surg 2002;124:1035-6.
3. Bronicki RA, Chang AC. Management of the postoperative pediatric cardiac surgical patient. Crit Care Med 2011;39:1974-84.
4. Angeli F, Verdecchia P, Karthikeyan G, Mazzotta G, Gentile G, Reboldi G. ß-Blockers reduce mortality in patients undergoing high-risk non-cardiac surgery. Am J Cardiovasc Drugs 2010;10:247-59.
5. Magee PG, Gardner TJ, Flaherty JT, Bulkley BH, Goldman RA, Gott VL. Improved myocardial protection with propranolol during induced ischemia. Circulation 1980;62:I49-56.
6. Quon CY, Stampfli HF. Biochemical properties of blood esmolol esterase. Drug Metab Dispos 1985;13:420-4.
7. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai CM. Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. Clin Pharmacol Ther 1983;34:427-34.
8. Cork RC, Kramer TH, Dreischmeier B, Behr S, DiNardo JA. The effect of esmolol given during cardiopulmonary bypass. Anesth Analg 1995;80:28-40.
9. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 2010;11:234-8.
10. Imura H, Caputo M, Parry A, Pawade A, Angelini GD, Suleiman MS. Age-dependent and hypoxia-related differences in myocardial protection during pediatric open heart surgery. Circulation 2001;103:1551-6.

11. Fellahi JL, Hedoire F, Le Manach Y, Monier E, Guillou L, Riou B. Determination of the threshold of cardiac troponin I associated with an adverse postoperative outcome after cardiac surgery: a comparative study between coronary artery bypass graft, valve surgery, and combined cardiac surgery. Crit Care 2007;11:106.
12. Immer FF, Stocker F, Seiler AM, Pfammatter JP, Bachmann D, Printzen G, et al. Troponin-I for prediction of early postoperative course after pediatric cardiac surgery. J Am Coll Cardiol 1999;33:1719-23.
13. Taggart DP, Hadjinikolas L, Hooper J, Albert J, Kemp M, Hue D, et al. Effects of age and ischemic times on biochemical evidence of myocardial injury after pediatric cardiac operations. J Thorac Cardiovasc Surg 1997;113:728-35.
14. Gupta-Malhotra M, Kern JH, Flynn PA, Schiller MS, Quaegebeur JM, Friedman DM. Cardiac troponin I after cardiopulmonary bypass in infants in comparison with older children. Cardiol Young 2013;23:431-5.
15. Watt K, Li JS, Benjamin DK Jr, Cohen-Wolkowiez M. Pediatric cardiovascular drug dosing in critically ill children and extracorporeal membrane oxygenation. J Cardiovasc Pharmacol 2011;58:126-32.
16. Gui P, Wu Q, Wu J, Yao S. Protective effect of esmolol on myocardial ischemic injury during open heart surgery in children. Paediatr Anaesth 2013;23:217-21.
17. Pieper GM, Todd GL, Wu ST, Salhany JM, Clayton FC, Eliot RS. Attenuation of myocardial acidosis by propranolol during ischaemic arrest and reperfusion: evidence with 31P nuclear magnetic resonance. Cardiovasc Res 1980;14:646-53.
18. Reynolds RD, Burmeister WE, Gorczynski RJ, Dickerson DD, Mathews MP, Lee RJ. Effects of propranolol on myocardial infarct size with and without coronary artery reperfusion in the dog. Cardiovasc Res 1981;15:411-20.
19. Becker LC, Fortuin NJ, Pitt B. Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. Circ Res 1971;28:263-9.
20. Wasserman DH, Lickley HL, Vranic M. Role of beta-adrenergic mechanisms during exercise in poorly controlled diabetes. J Appl Physiol 1985;59:1282-9.
21. Lell WA, Pearce FB. Tetralogy of fallot. In: Lake CL, Booker PD, editors. Pediatric cardiac anesthesia. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 344-56.