Relation of Troponin I Levels with Postoperative Mortality and Morbidity Rates in Patients Followed in Intensive Care Unit After Congenital Cardiac Surgery Whose Ages Between 7 Days and 16 Years Old

Hülya Yılmaz Ak[1], Mustafa Yıldız[2], Nurgül Yurtseven[3], Deniz Özsoy[4], Doğaç Okşen[2], Hakkı Kürşat Çetin[4]

[1] University of İstanbul Cardiology Institute, Department of Anesthesiology and Intensive Care, İstanbul, Turkey
[2] University of İstanbul Cardiology Institute, Department of Cardiology, İstanbul, Turkey
[3] İstanbul Dr. Siyami Ersek Chest and Cardiovascular Surgery Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[4] University of İstanbul Cardiology Institute, Department of Cardiovascular Surgery, İstanbul, Turkey

ABSTRACT

Introduction: Troponin I levels are the most important predictive marker of myocardial injury. Myocardial injury has been reported as the most significant cause of morbidity and mortality in pediatric cardiac surgery. In this study, we aimed to evaluate the effect of troponin I on postoperative mortality and morbidity in the child population.

Patients and Methods: Ninety-nine patients to whom congenital cardiac surgery were included in this study. Perioperative and postoperative troponin I values at 24th and 48th hours were recorded. Patients were divided into two groups according to troponin I values at 24th hour (lower and higher than 15 ng/mL, respectively). Aortic cross-clamp time, cardiopulmonary bypass (CPB) time, intubation time, and the duration of intensive care unit stay and medication of inotropic agents were recorded.

Results: Postoperative troponin I levels at 24th hour were higher than 15 ng/mL in patients who underwent congenital cardiac surgery and were related with significantly higher CPB, aortic cross-clamp, intubation time, and longer stay in intensive care unit.

Conclusion: Higher troponin I levels at 24th hour are associated with increased morbidity in patients who undergo congenital cardiac surgery.

Key Words: Congenital cardiac surgery; troponin I; mortality; morbidity

Konjenital Kardiyak Cerrahi Sonrası Yoğun Bakım Ünitesinde Takip Edilen 7 Gün ile 16 Yaş Aralığındaki Hastalarda Troponin I Seviyelerinin Postoperatif Mortalite ve Morbidite ile İlişkisi

ÖZET

Giriş: Troponin I miyokardiyal hasarın tahmininde önemli bir belirteçtir. Pediyatrik kardiyak cerrahide miyokardiyal hasarın en önemli mortalite ve morbidite nedeni olduğu anlaşılmıştır. Bu çalışma ile konjenital kalp ameliyatı olan çocuklarda troponin I değerlerinin postoperatif mortalite ve morbidite üzerine etkisini değerlendirmek amaçlanmıştır.

Hastalar ve Yöntem: Konjenital kardiyak cerrahi uygulanan 99 hastanın perioperatif, postoperatif 24. ve 48. saatteki troponin I değerleri kaydedildi. Hastalar hesaplanan cut off değerine göre 24. saat troponin I seviyelerine göre iki gruba ayrıldı (15 ng/mL'den yüksek olanlar ve olmayanlar). Hastaların aortik kros klemp süreleri, kardiyopulmoner baypas süresi, entübasyon süresi, yoğun bakımda kalış süresi ve inotropik ajan düzeyleri kaydedildi.

Bulgular: Konjenital kalp ameliyatı olan hastalarda postoperatif 24. saatte ölçülen troponin I seviyelerinin 15 ng/mL'nin üzerinde olmasının: kardiyopulmoner baypas süresi, aortik kross klamp süresi, entübasyon süresi ve yoğun bakım kalış süresini anlamlı olarak arttırdığı gösterildi.

Sonuç: Konjenital kalp ameliyatı olan hastalarda postoperatif 24. saat yüksek troponin I düzeyleri yüksek morbidite riski ile uyumludur.

Anahtar Kelimeler: Konjenital kalp ameliyatı; mortalite; morbidite; troponin I

Correspondence

Doğaç Okşen

E-mail: dogacoksen@gmail.com
Submitted: 15.09.2017
Accepted: 28.09.2017

INTRODUCTION

With technological improvement in anesthesia of cardiac surgery, cardiopulmonary bypass (CPB), and continuation of extracorporeal circulation, there has been significant development in pediatric and adult cardiac surgery. It is well known that myocardial injury secondary to surgery or CPB affects cardiac functions, therefore increase morbidity and mortality[1].

Pediatric open heart surgery is a special operation that has different success rates depending on the quality of technique. Intraoperative myocardial tissue injury affects postoperative cardiac functions which is directly related with morbidity and mortality[2].

Cardiac troponins are sensitive and specific markers for myocardial injury. High specificity of troponin is derived from specific isoforms of cardiac troponin T and I. Therefore, creatine kinase (CK) and creatine kinase MB (CK-MB) associated with skeletal muscle but are not relevant with cardiac troponins[3,4]. Several studies have shown that cardiac troponin I levels are safe can be used as an indicator of myocardial damage both in pediatric and adult cardiac surgery. Increased troponin I levels have been associated with postoperative complications like delayed extubation time, necessity of higher inotropic support, and mortality[5-7].

In this study, we aimed to evaluate the effects of troponin I on postoperative mortality and morbidity in patients between 7 days and 16 years old who underwent congenital cardiac surgery.

PATIENTS and METHODS

This study has been approved by Institutional Review Board.

Study Subjects

Ninety-nine patients between 7 days and 16 years old, who were operated in Siyami Ersek Thoracic and Cardiovascular Surgery Center due to congenital cardiac disease, were included in this study. Patients who had liver and kidney failure were excluded. The indications for operation were as follows: transposition of the great arteries (TGA) (n= 14), atrioventricular canal defect (AVCD) (n= 6), Glenn shunt (n= 2), ventricular septal defect (n= 34), atrial septal defect (n= 7), tetralogy of Fallot (TOF) (n= 18), cor atrium (n= 1), anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) (n= 2), double outlet right ventricle (DORV) (n= 4), supravalvular aort stenosis (n= 2), truncus arteriosus (n= 1), total anomalous pulmonary venous connection (TAPVD) (n= 3), VSD and aortic coarctation (n= 1), AVCD and DORV (n= 1), VSD and ASD (n= 1), supraaortic ridge (n= 3).

All subjects gave their consent for inclusion in the study. The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee.

Anesthesia and Surgical Protocol

All patients included in the study underwent the same anesthesia protocol. For sedation 3-5 mg/kg intramuscular (IM) ketamine was performed; afterward arterial line and venous angiocatheter was inserted. We administered 0.1 mg/kg intravenous (IV) midazolam, 5-10 μg/kg Fentanyl (IV), 0.1 μg/kg Vecuronium (IV) for induction of anesthesia. To maintain anesthesia during the operation, before and after CPB 0.1 mcg/kg/m Fentanyl and Sevoflurane, during CPB in every 30 minutes 0.5-1 mg Vecuronium, 5-10 μg/kg Fentanyl and 0.5-1 mg midazolam were performed.

Following sternotomy, standard aortic and bicaval cannulation was administered. Activated clotting time was held over 400 seconds by 300 U/kg heparin IV infusion. CPB membrane oxygenator (Minimax Plus, Medtronic Inc., Minneapolis, MN USA) and roller pump (Sarns Inc. USA) were used. Primary solution was prepared with lactate, whole blood (to hold hematocrit over 20%), albumin 20%, mannitol, and heparin. After cross-clamping aorta, to save myocardial tissue, blood cardioplegia at 4°C with an initial dose of 20 mL/kg and maintenance in every 20 minutes 10 mL/kg were performed. Ultrafiltration was applied starting from warming period of CPB.

Design of the Study

Blood samples for troponin I levels were taken from all patients on preoperative, postoperative 1st, 24th, and 48th hours. The following data below were recorded.

- Duration of aortic cross-clamp and operation time.
- Lactate levels of pre-operative, 1st, 24th, and 48th hours.
- Levels of inotropic agents performed after CPB was determined by Vasoactive-Inotropic Score.
- Inotropic score= [dopamine (μg/kg/min) + dobutamine (μg/kg/min) + adrenalin (μg/kg/min) x 100]
- Duration of mechanical ventilation and stay in intensive care unit.

Statistical Analysis

Number Cruncher Statistical System 2007 (NCSS), Power Analysis & Sample Size 2008 (PASS), Statistical Software 2008 (Utah, USA) programs were used in this study. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used in statistical evaluation. Student's t-test was performed for comparison of normally distributed variables and Mann-Whitney U test was used for the parameters that were not normally distributed. The repeated Measures repeated measures analysis of variance (ANOVA) for normally distributed in-group comparison and corrected Bonferroni test for binary comparisons were used. Freidman test was used to compare groups that were not normally distributed, and Wilcoxon Signed Ranks were applied for binary comparisons. ROC analysis and diagnostic screening tests were used to detect cut-off points according to the presence of morbidity and/or mortality. Significance was assessed at $p< 0.01$ and $p< 0.05$.

RESULTS

The study was composed of 99 patients, and 49.5% (n= 49) of the participants were female. The median age of the patients was 38 ± 41.9 months (range; 26-192). The distributions of descriptive properties of the cases are shown in Table 1. Mortality was observed in 3% (n= 3) of the patients.

Preoperative and postoperative 1st, 24th, and 48th hours troponin I levels are demonstrated in Table 2 and Figure 1.

Table 1. Distribution of descriptive features

	Min-Max	Mean ± SD
Age (month)	0.26-192.0	38.07 ± 41.95
Cross time (minute)	16.0-223.0	74.89 ± 44.42
Bypass time (minute)	31.0-323.0	105.05 ± 58.62
Intubation time in ICU (hour)	2.0-504.0	48.13 ± 79.35
ICU stay (day)	1.0-31.0	4.68 ± 5.46
	n	**%**
Gender		
Female (1)	49	49
Male (2)	50	50
Mortality		
Survival	96	96
Exitus	3	3
Inotropic agents		
0	5	5.1
1	19	19.2
2	38	38.4
3	27	27.3
4	10	10.1

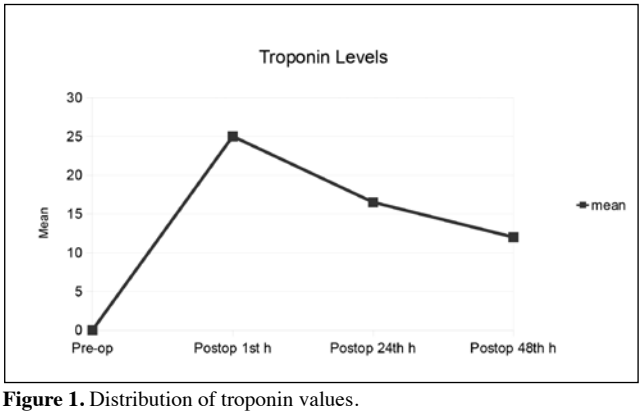

Figure 1. Distribution of troponin values.

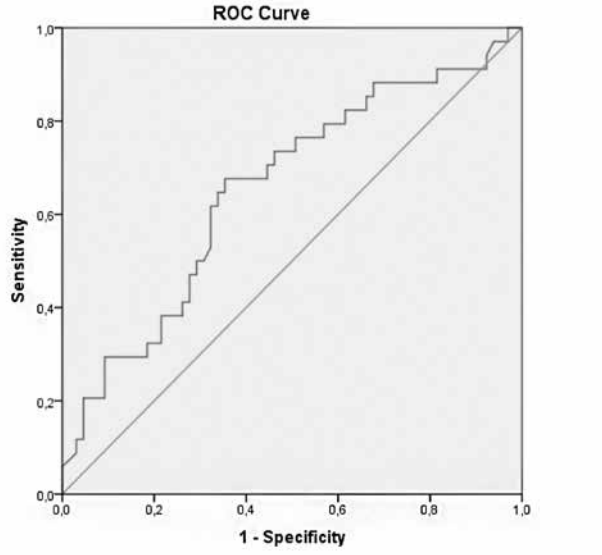

Figure 2. ROC curve of 24th hour troponin levels in morbidity and/or mortality.

The changes of preoperative, postoperative 1st, 24th, and 48th hours Troponin I levels were statistically significant (p= 0.001; p< 0.01). The increase in postoperative 1st, 24th, and 48th hours troponin levels were significantly higher than the preoperative levels (p= 0.001; p= 0.001; p= 0.001; p< 0.01, respectively). Postoperative 24th and 48th hours troponin I levels were in decreasing trend when compared to preoperative levels (p= 0.001; p= 0.001; p< 0.01, respectively). Postoperative 48th hour levels were siginificantly lower than 24th hour levels (p= 0.001; p< 0.01).

The 24th hour troponin levels were significantly different (p= 0.012; p< 0.05) and troponin levels in 24th hour were notably higher (Table 3). Based on this data, ROC analysis for 24th hour Troponin levels and cut-off values for diagnostic screening tests were calculated.

The cut-off point of 24th hour troponin level for prediction of morbidity and mortality was 15 with a sensitivity of 58.82%; specificity of 67.69%; positive predictive value of 48.78%; and negative predictive value of 75.86% (Table 3). Area under ROC curve was 65.5% with 5.9% standard deviation (Figure 2). Postoperative 24th hour troponin I levels are demonstrated in Table 4. The cross-clamping, bypass, intubation, and intensive care stay time were significantly shorter in the group with troponin levels < 15 in the postoperative 24th hour compared with those with troponin levels ≥ 15 (p< 0.05).

The patients who had intensive care unit staying time shorter than 5 days had significantly lower postoperative 24th hour troponin levels than those with longer stays (p= 0.029; p< 0.05) (Table 5).

Table 2. Troponin values

Troponin (ng/mL)	Min-Max	Mean ± SD (median)	[a]p	[b]Post-hoc
[1]Pre-op	0.00-50.00	0.91 ± 5.39 (0.02)	0.001**	1 < 4 < 3 < 2
[2]Post-op 1st hour	0.07-98.0	24.82 ± 23.30 (17.50)		
[3]Post-op 24th hours	0.99-84.51	16.55 ± 15.18 (12.21)		
[4]Post-op 48th hours	0.00-153.00	11.65 ± 19.57 (6.83)		

** p< 0.01
[a] Friedman test,
[b] Wilcoxon signed ranks test

Table 3. Diagnostic scanning features of 24th hour troponin levels and analysis of ROC curve

	Diagnostic Scan	ROC Curve	p					
	Cut off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
24th hours troponin levels	≥ 15	58.82	67.69	48.78	75.86	0.655	0.552-0.747	0.009*

* Mann-Whitney U test

Table 4. Evaluation of postoperative 24th hour troponin I levels

	Postop 24th hours Troponin < 15 ng/mL (n= 58)	Postop 24th hours Troponin ≥ 15 ng/mL (n= 41)	p
	Mean ± SD	Mean ± SD	
Cross time (min); (median)	64.51 ± 38.47 (52.50)	89.56 ± 48.46 (80.00)	[e]0.003**
Bypass time (min); (median)	90.46 ± 46.42 (75.50)	125.68 ± 67.86 (109.00)	[e]0.003**
Intubation time (hour); (median)	31.50 ± 42.82 (12.00)	72.86 ± 110.02 (24.00)	[e]0.022*
ICU staying time (day); (median)	3.53 ± 3.60 (2.15)	6.31 ± 7.06 (4.00)	[e]0.003**

* p< 0.05
** p< 0.01
[e] Mann-Whitney U test

Table 5. Relation between postoperative 24th hour troponin levels and morbidity

	Morbidity (-) (n= 66)	Morbidity (+) (n= 33)	p
	Mean ± SD (median)	Mean ± SD (median)	
Postop 24th hour troponin	14.22 ± 13.26 (10.35)	21.22 ± 17.74 (16.20)	0.029*

* p< 0.05
Mann-Whitney U test

Table 6. Relation between postoperative 24th hour troponin levels and morbidity and/or mortality

	Morbidity and/or mortality		p
	No (n= 65) Mean ± SD (median)	Yes (n= 34) Mean ± SD (median)	
Postoperative 24th hour troponin	13.48 ± 11.93 (10.24)	22.42 ± 18.82 (16.42)	0.012*

* p< 0.05
Mann-Whitney U test

Table 7. Troponin levels and mortality rates

Troponin	Mortality		p
	No (n= 65) Mean ± SD (median)	Yes (n= 34) Mean ± SD (median)	
Preop	0.94 ± 5.47 (0.02)	0.02±0.01 (0.02)	0.603
Postop 1st hour	24.12 ± 22.42 (16.97)	47.12 ± 44.23 (25.60)	0.198
Postop 24th hours	16.03 ± 14.67 (11.72)	33.31 ± 25.15 (22.80)	0.086
Postop 48th hours	10.50 ± 17.54 (6.59)	48.75 ± 44.91 (38.19)	0.023

* p< 0.05
Mann-Whitney U test

The cases without any morbidity and/or mortality had significantly lower 24th hour troponin levels than those who suffered morbidity and/or mortality (p= 0.012; p< 0.05) (Table 6).

Regarding the mortality rates, there was no statistically significant difference between preoperative, postoperative, 1st, and 24th hours troponin levels (p> 0.05). However, postoperative 48th hour Troponin levels were significantly higher in deceased patients than the survivors (p< 0.023; p< 0.05) (Table 7).

DISCUSSION

The heart, in pediatric population, faces more metabolic changes when exposed to ischemia, cardioplegic arrest, and reperfusion. Myocardial injury was demonstrated to be the most important reason of mortality and morbidity in pediatric cardiac surgery[5-8]. Therefore, operator should pay attention to protect myocardial tissue in congenital cardiac surgery. The presence of complex defects and intervention to more than one anomaly affect morbidity and mortality[9].

Troponin T and I have been found to be more specific in pediatric cardiac surgery rather than CK-MB and myoglobin in determining myocardial tissue injury[8,9].

Data regarding troponin T and I for diagnosis and follow up of infantile and pediatric population have recently been reported. Previous studies demonstrated the superiority of Troponin I to Troponin T in determining myocardial injury after surgery[10-12]. Therefore, we preferred troponin I in our study as it reflects injury better. According to troponin I cut-off values of 15 ng/mL at postoperative 24th hour, we classified patients into two groups. In our study, the highest troponin I levels were recorded in the postoperative 24th hour[13].

Immer et al. performed a study in 73 patients who underwent congenital cardiac surgery[14]. Patients were assigned in two groups according to postoperative 24th hour troponin I levels (higher or lower than 35 ng/mL). The group with higher troponin levels significantly had more liver and kidney dysfunction, necessity of vasoactive agents, and longer intubation times[14]. In our study, the patients with postoperative 24th hour troponin I levels higher than 15 ng/mL, had significantly longer intubation time. Contrary to findings reported by Immer et al.[14], there was no statistically significant difference relationship between troponin I levels and necessity of inotropic agents in our study.

Several studies demonstrated that troponin I level higher than 100 ng/mL was related with increased mortality in pediatric population[12,14,15]. However, recently studies pointed out that high troponin levels were not associated with high cardiovascular risk or mortality in infants who underwent congenital cardiac surgery[16,17].

In our study, troponin levels were found under 100 ng/mL in 2 of the 3 deceased patients. Troponin values of these patients in postoperative 48th hour were significantly higher compared with remaining living patients. Consequently, troponin levels continued to stay higher in patients who ended up with mortality.

Recent studies showed that variety of congenital cardiac disorders and surgery altered troponin levels[8,12,18]. Imura et al.

stated that troponin I levels, aortic cross-clamp and CPB time, and frequency of postoperative inotropic medication were significantly higher in complex TGA group than basic TGA in pediatric population[18]. This difference was related with myocardial injury due to incision. In our study, aortic cross-clamp time and duration of bypass were significantly longer in patients who had troponin I levels higher than 15 ng/mL in postoperative 24th hour.

Previous studies pointed out the relation of higher postoperative troponin I levels with major complications in adult cardiovascular surgery[1]. Following pediatric surgery, intubation and intensive care unit stay time which have effects on morbidity and mortality, were found significantly longer, as shown in our study[19]. Despite, high levels of troponin I in infant population; Bojan et al. declared the unnecessity of routine troponin I use in infants under 1 years old [12,13,20].

Consequently, the use of cardiac markers has been increasing during treatment of patients with congenital heart disease; however, there is no valid guideline regarding the routine use of these markers. Troponin I is one of the most significant markers establishing myocardial injury in congenital cardiac surgery. In our study, postoperative 24th hour Troponin I levels higher than 15 ng/mL were significantly related with longer CPB, aortic cross-clamp, intubation, and intensive care unit staying time in patients who underwent congenital cardiac surgery. Routine use of troponin I during follow up in congenital cardiovascular surgery may be useful in estimation of postoperative morbidity and mortality.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article

AUTHORSHIP CONTRIBUTIONS

Concept/Design: DO

Analysis/Interpretation: ŞDÖ, HYA

Data Acquisition: HYA

Writting: DÖ, HYA, MY

Critical Revision: HKC, ŞDÖ

Final Approval: All of authors

REFERENCES

1. Lasocki S, Provenchère S, Bénessiano J, Vicaut E, Lecharny JB, Desmonts JM, et al. Cardiac troponin-I is an independent predictor of in-hospital death after adult cardiac surgery. Anesthesiology 2002;97:405-11.
2. Moon MH, Song H, Wang YP, Jo KH, Kim CK, Cho KD. Changes of cardiac troponin I and operative mortality of coronary artery bypass. Asian Cardiovasc Thorac Ann 2014;22:40-5.
3. Wu AHB. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? Intensive Care Med 2001;27:959-61.
4. Jaffe AS. Biomarker odyssey. Clin Chim Acta 1999;284:197-211.
5. Flyer D. Report on the New England regional infant cardiac Program. Pediatrics. 1980;65:375-461.
6. Mildh LH, Pettilä V, Sairanen HI, Rautiainen PH. Cardiac Troponin T levels for risk stratification in pediatric open heart surgery. Ann Thorac Surg 2006;82:1643-9.
7. Montgomery VL, Sullivan JE, Buchino JJ. Prognostic value of pre-and postoperative cardiac Troponin I measurement in children having cardiac surgery. Pediatr Dev Pathol 2000;3:53-60.
8. Taggart DP, Hadjinikolas L, Wong K, Yap J, Hooper J, Kemp M, et al. Vulnerability of pediatric myocardium to cardiac surgery. Heart 1996;76:214-21.
9. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, et al. Predictive value of cardiac Troponin T pediatric patiens at risk for myocardial injury. Circulaton 1997;96:2641-8.
10. Immer FF, Stocker FP, Seiler AM, Pfammatter JP, Printzen G, Carrel TP. Comparison of Troponin-I and Troponin-T after pediatric cardiovascular operation. Ann Thorac Surg 1998;66:2073-7.
11. Hirsch R, Dent CL, Wood MK, Huddleston CB, Mendeloff EN, Balzer DT, et al. Patterns and potential value of cardiac Troponin I elevations after pediatric cardiac operations. Ann Thorac Surg 1998;65:1394-9.
12. 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.
13. Bojan M, Peperstraete H, Lilot M, Vicca S, Pouard P, Vouhé P. Early elevation of cardiac troponin I is predictive of short-term outcome in neonates and infants with coronary anomalies or reduced ventricular mass undergoing cardiac surgey. J Thorac Cardiovasc Surg 2012;144:1436-44.
14. 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.
15. Bottio T, Vida V, Padalino M, Gerosa G, Stellin G. Early and long-term prognostic value of Troponin-I after cardiac surgery in newborns and children. Eur J Cardiothorac Surg 2006;30:250-5.
16. 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.
17. Momeni M, Poncelet A, Rubay J, Matta A, Veevaete L, Detaille T, et al. Does postoperative cardiac troponin-ı have any prognostic value in predicting midterm mortality after congenital cardiac surgery? J Cardiothorac Vasc Anesth 2017;31:122-7.
18. Imura H, Modi P, Pawade A, Parry AJ, Suleiman MS, Angelini GD, et al. Cardiac Troponin I in neonates undergoing the arterial switch operation. Ann Thorac Surg 2002;74:1998-2002.
19. Modi P, Imura H, Angelini GD, Pawade A, Parry AJ, Suleiman MS, et al. Pathology-related Troponin I release and clinical outcome after pediatric open heart surgery. J Card Surg 2003;18:295-300.
20. Saraiya NR, Sun LS, Jonassen AE, Pesce MA, Queagebeur JM. Serum cardiac Troponin-I elevation in neonatal cardiac surgery is lesion-dependent. J Cardiothorac Vasc Anesth. 2005;19:620-5.