The Acute Cardioprotective Effect of Glucocorticoid in Myocardial Ischemia-Reperfusion Injury Occuring During Cardiopulmonary Bypass

KARDİYOPULMONER BYPASS ESNASINDA ORTAYA ÇIKAN MİYOKARDİYAL İSKEMİ-REPERFÜZYON HASARINA KARŞI GLUKOKORTİKOİDLERİN KARDİYOPROTEKTİF ETKİLERİ

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Abstract

Objective: The purpose of this study was to evaluate the acute cardioprotective effect of high dose methylprednisolone (25 mg/kg) in the controlled in vivo model of myocardial ischemia-reperfusion injury occurring during cardiopulmonary bypass.

Material and Methods: Forty non-diabetic male patients with three-vessel disease undergoing primary bypass surgery were enrolled in this double blind prospective study. Patients were randomized to either methyprednisolone 25 mg/kg (group I) or saline (group II) one hour prior to cardiopulmonary bypass. The levels of cardiac troponin-I (cTnI) were used as a marker of myocardial tissue damage in myocardial-ischemia reperfusion injury. The cTnI levels were measured prior to surgery, at 2 hours following cardiopulmonary bypass, at postoperative hour 6 and 24 and day 5.

Results: There was no significant difference between the two groups with respect to the duration of ischemia and reperfusion. The preoperative cTnI levels were 0.22 ± 0.29 ng/ml in Group I and 0.23 ± 0.28 ng/ml in group II. cTnI levels increased to 0.40±1.0 ng/ml in group I and 3.19±0.88 ng/ml in group II at the 2nd hour after cardiopulmonary bypass. The differences between T1 and T0 levels that showed the amount of troponin release occurring due to ischemia-reperfusion injury were calculated and compared. There was a significant difference between group I and group II (p= 0.024). The cTnI levels measured at postoperative hour 6 were 1.98±0.63 ng/ml in group I and 2.75 ± 1.15 ng/ml in group II (p= 0.049). cTnI levels decreased to 0.22 ± 0.10 ng/ml in group I and 0.49 ± 0.25 ng/ml in group II on postoperative day 5 (p= 0.0001). Univalent regression analysis showed that preoperative high dose corticosteroid use decreased the troponin release for about 12% and this effect was statistically significant (r^2: 0.12, p< 0.05)

Conclusion: Single dose of intravenous methylprednisolone (25 mg/kg) administered one hour prior to ischemia reduced myocardial ischemia-reperfusion injury. These results suggest that the acute cardioprotective effect of corticosteroids in decreasing ischemia-reperfusion injury occurring during cardiopulmonary bypass surgery seems to be promising.

Key Words: Corticosteroids, myocardium, ischemia-reperfusion injury

Özet

Amaç: Bu çalışmanın amacı, yüksek doz metilprednisolonun (25 mg/kg) akut kardiyoprotektif etkilerinin kardiyopulmoner bypass sırasında oluşan miyokardiyal iskemi-reperfüzyon hasarı modelinde değerlendirilmesidir.

Gereç ve Yöntemler: Bu çift kör prospektif çalışmaya ilk defa bypass olacak 3 damar hastası diyabetik olmayan 40 erkek hasta dahil edilmiştir. Hastalar, kardiyopulmoner bypasstan 1 saat önce 25 mg/kg metilprednisolon (grup I) veya salin solüsyonu (grup II) verilecek olarak rastgele 2 gruba ayrıldı. Miyokardiyal iskemi-reperfüzyon hasarındaki miyokardiyal doku hasarını göstermek amacıyla kardiyak Troponin-I (cTnI) seviyeleri kullanıldı. cTnI seviyeleri cerrahiden önce, kardiyopulmoner bypasstan 2 saat sonra, postoperatif 6. saat ve postoperatif 5. günü ölçüldü.

Bulgular: İki grup arasında iskemi ve reperfüzyon süresi bakımından bir fark bulunamadı. Preoperatif cTnI seviyeleri grup I için 0.22 ± 0.29 ng/mL ve grup II için ise 0.23 ± 0.28 ng/mL olarak bulundu. Kardiyopulmoner bypassı takip eden 2. saatte cTnI seviyeleri grup I'de 2.40 ± 1.0 ng/mL'ye, grup II'de ise 3.19 ± 0.88 ng/mL'ye yükseldi (p= 0.015). İskemi-reperfüzyon hasarı nedeni ile salınan troponin miktarını gösteren T1 ile T0 arasındaki fark hesaplandığında ve karşılaştırıldığında, grup I ile grup II arasında istatistiksel olarak anlamlı bir farkın varlığı tespit edildi (p= 0.024). Altıncı saatte cTnI seviyeleri grup I ve II için sırasıyla 1.98 ± 0.63 ng/mL ve 2.75 ± 1.15 ng/mL olarak ölçüldü (p= 0.049). Postop 5. günde ise cTnI seviyeleri grup I'de 0.22 ± 0.10 ng/mL'ye ve grup II'de 0.49 ± 0.25 ng/mL'ye geriledi (p= 0.0001). Univaryant regresyon analizi; kardiyopulmoner bypass cerrahisi geçiren koroner arter hastalığında preoperatif yüksek doz kortikosteroid kullanımında troponin salınımını %12 düzeyinde azalttığını ve bu etkinin istatistiksel olarak anlamlı olduğunu gösterdi (r^2: 0.12, p< 0.05).

Sonuçlar: İskemiden 1 saat önce tek doz iv metilprednisolon (25 mg/kg) verilmesi miyokardiyal iskemi-reperfüzyon hasarını azaltır. Bu sonuçlar ışığında; kardiyopulmoner bypass esnasında görülen iskemi-reperfüzyon hasarını azaltmada kortikosteroidlerin akut kardiyoprotektif etkilerinin gelecek için umut verici olduğu görülmüştür.

Anahtar Kelimeler: Kortikosteroidler, miyokard, iskemi-reperfüzyon hasarı

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Ischemia damages myocardial tissue both during the initial ischemia and the subsequent reperfusion of myocardium with oxygen. Indeed, the regimen of high dose corticosteroid protects the heart from ischemia-reperfusion injury.[1,2]

However, corticosteroids are no longer used in myocardial ischemia because of their potential adverse affects on the cardiovascular system, many of which are observed with chronic use and are probably mediated by genomic mechanisms that inhibit wound healing and remodeling of cardiomyocytes.[3] However, defining the nuclear and non-nuclear actions of corticosteroids could have important therapeutic implications particularly in coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass (CPB) in which myocardial ischemia inevitably occurs even under optimal myocardial protection during aortic cross-clamp. Besides, the use of CPB that induces systemic inflammatory reaction, contributes to the final activation of leucocytes and endothelial cells, which are also responsible for cell dysfunction in the myocardium and various other organs.

Since the original description of the measurement of cardiac troponin T (cTnT) by Katus et al. in 1989 and subsequently of cardiac troponin I (cTnI) there has been a revolution in the technology for cardiac marker measurement.[4,5] The advantage of cTn lies in their ability to provide a cardiospecific diagnosis. A much more specific and sensitive method for detection of perioperative myocardial ischemic injury is now available.[6,7] Thus, we measured the levels of cTnI as a marker of myocardial tissue damage occurring during CPB.

The purpose of this study was to test the hypothesis that high dose of intravenous (IV) methylprednisolone (25 mg/kg) administration 1 hour before CPB correlates with a lesser degree of myocardial injury as measured by a decrease in cTnI release.

Material and Methods

After institutional ethics committee approval, 40 non-diabetic male patients with three-vessel disease undergoing primary bypass surgery were enrolled for this double blind randomized prospective study. Informed consent vas obtained from all patients. Patients were randomly assigned to 25 mg/kg methylprednisolone (MP) IV (group I) or saline (group II) 1 hour before CPB.

Anesthesia was standardized for all patients and was induced by fentanyl (Fentanyl-Janssen) 15 μg/kg and propofol 2 mg/kg. Endotracheal intubation was facilitated by pancuronium 0.1 mg/kg. Anesthesia was maintained with sevoflurane 1% to 2% in 3 L/min of oxygen and fentanyl infusion. Before the cannulation, heparin (Liquemin) 3.5 mg/kg was administered. Membrane oxygenator and centrifugal pump were used during CPB. The surgical and bypass procedures were also standardized. Cardiac arrest was provided by the use of hypercalemic cold (4°C) blood cardioplegia 10 ml/kg as the initial dose (1 L Blood, 20 mEq K^+, 16 mEq HCO_3, 7.364 mg/L citrate, 16 mMol/L Mg^{++} and 1 gr/L glucose). During the cross-clamping, cardioplegic solution administration (5 ml/kg) was repeated every 20 minutes. Patients were cooled to a rectal temperature of 28°C. Complete revascularization was performed in all patients. All patients were separated from CPB uneventfully. Heparin was neutralized with protamine hydrochloride at a ratio of 1:1.3 after CPB ceased.

The levels of cTnI were used as a marker of myocardial tissue damage in myocardial ischemia-reperfusion injury occurring during CPB. cTnI analysis was performed using Access Immunoassay System Auto-analyzer (Beckman Coulter Corporation, USA) and the cTnI levels were measured before surgery, at 2 hours after CPB, at postoperative 6 and 24 hours and on day 5.

All analyses were performed using the Statistical Package for the Social Sciences, Version 11.0 (SPSS Inc, Chicago, III). Data were expressed as mean ± standart deviation (SD).

Pre- and perioperative variables were compared by using Mann-Whitney U test. Regarding the cTnI values, the distribution of T0, T1, T2, T3 and T4 values was abnormal and the variation was not homogenous. However, as the level of myocardial ischemia-reperfusion injury occurring during CPB was best expressed by the differences between T1 and T0. These values were also calculated for each group. The distribution of these val-

ues was normal and the variation was homogenous. Therefore, while the differences between both groups at times T0, T1, T2, T3 and T4 were assessed by the Mann-Whitney U test; the Student's *t* test was used to evaluate the differences between values calculated as the differences between T1 and T0. Then univariate regression analysis was used to assess the degree of steroid effect on postoperative troponin release calculated as the differences between T1 and T0.

Results

There were no significant differences between the two groups with respect to pre- and perioperative variables such as the cross-clamp times, CPB times, preoperative cTnI levels and the ages of the patients (Table 1).

All patients enrolled for this double blind randomized prospective study were separated from CPB uneventfully. None of them received mechanical or inotropic support. While the preoperative cTnI levels were 0.22 ± 0.29 ng/ml in group I and 0.23 ± 0.28 ng/mL in group II, cTnI levels increased to 2.40 ± 1.0 ng/mL in group I and 3.19 ± 0.88 nf/mL in group II at 2 hours after complete myocardial revascularization with CPB (Table 2). There was a significant difference between the two groups regarding cTnI levels during early reperfusion period; the cTnI level was significantly lower in patients who received high dose methylprednisolone 1 hour before CPB (p= 0.015). Besides, considering the amount of troponin release due to ischemia-reperfusion injury occurring during CPB calculated as the differences between T1 and T0 there was also significant differences between group I and group II (p= 0.024). In spite of decreasing the significance, cTnI levels were still significantly lower in group I than in group II at 6 hours of the reperfusion period (p= 0.049). Although cTnI level measured at 24 hours showed no significant differences, there was a significant difference between the two groups in the cTnI levels measured on postoperative day 5 (p= 0.0001). cTnI levels on postoperative day 5 were also significantly lower in patients who received high dose methylprednisolone before CPB.

In the evaluation of the level of myocardial ischemia-reperfusion injury occurring during CPB that was measured as the difference between T1 and T0, univariant regression analysis showed that preoperative high dose corticosteroid usage

Table 1. Pre- and perioperative variables of the patients.

	Group I (#: 20)	Group II (#: 20)	p
Age (years)	60.1 ± 9.9	56.6 ± 9.1	NS
Weight (kg)	81.1 ± 4.6	81.3 ± 3.7	NS
Height (cm)	170.4 ± 2.6	172.8 ± 2.6	NS
CC time (minutes)	51.35 ± 8.4	52.3 ± 3.6	NS
CPB time (minutes)	78.3 ± 8.8	79.2 ± 13.3	NS

NS: nonsignificant, CC time: Cross clamp time,
CPB time: Cardiopulmonary bypass time.

Table 2. Preoperative and postoperative cTnI levels of the patients.

	cTnI level (ng/mL)		
Sample time	**Group I (n= 20)**	**Group II (n= 20)**	**p**
Preoperative	0.22 ± 0.29 (T0)	0.23 ± 0.28 (T0)	NS
At 2 hr after CPB	2.40 ± 1.02 (T1)	3.19 ± 0.88 (T1)	0.015
The difference (T1-T0)	2.17 ± 1.04	2.96 ± 1.06	0.024
At 6 hr after CPB	1.98 ± 0.63	2.75 ± 1.15	0.049
At 24^{h} hr after CPB	0.92 ± 0.39	1.20 ± 0.88	NS
On postoperative day 5	0.22 ± 0.10	0.49 ± 0.25	0.0001

NS: Non-significant; CPB: Cardiopulmonary bypass; hr: hours.

decreased the troponin release for about 12% and this effect was statistically significant (r^2: 0.12, p= 0.024).

Thirty five patients were discharged from the hospital at postoperative day 5 without any infection and wound problem. Postoperative atrial fibrillation (AF) occurred in 5 patients. Therefore, 2 patients in group I and 3 patients in group II were discharged from the hospital at postoerative day 7 due to the occurrence of postoperative AF.

Discussion

Recent reports show that corticosteroids exert acute beneficial effect in myocardial ischemia-reperfusion injury.[8] In the present study, the acute cardioprotective effect of corticosteroids was tested in the in vivo myocardial ischemia-reperfusion injury model occuring during CPB. This study also showed that high dose of methylprednisolone (25 mg/kg) administered 1 hour before ischemia occurring during aortic cross-clamp period significantly decreased the myocardial tissue damage occurring during reperfusion.

Corticosteroids have a variety of actions through binding to the glucocorticoid receptor. When bound to corticosteroids, steroid receptor modulates the expression of target genes by binding the DNA sequences containing the glucocorticoid response elements (GRE).[9] However, it was recently found that some anti-inflammatory effect of glucocorticoids occur via non-GRE (non-nuclear) mediated effects on prostoglandin synthesis and nuclear factor $_k$B (NF-$_k$B) activation.[8] Corticosteroids decrease NF-$_k$B activation that controls the expression of adhesion molecules. On the other hand, the recently demonstrated cardioprotective effect mediated by GR-bound corticosteroids is the rapid, non-transcriptional activation of endothelial nitric oxide synthase (eNOS) through activation of phosphatidylinositol 3-kinase (PI3 kinase) and protein kinase B (c-AKT).[8] Endothelium derived nitric oxide (NO) is an important endogenous mediator of cardiovascular protection.[10] NO produced by endothelial NO synthase (eNOS) possesses anti-inflammatory, anti-atherogenic and anti-ischemic properties.[11.] Moreover, corticosteroids also induce the expression of Annexin-1, which is a calcium-dependent phospholipid binding protein. Annexin-1 inhibits the infiltration of neutrophils into tissue, blocking reperfusion-induced inflammatory heart damage.[12-14]

Myocardial injury causing stunning after CPB has also been associated with an enhanced inflammatory response.[15-17] Such findings suggest a pivotal role of acute phase reaction in the pathogenesis of myocardial injury and stunning. Zahler et al pointed out the presence of a transcardiac veno-arterial difference of plasma levels in interleukin-6 (IL-6) rising from 0.1 to 110 pg/mL after 75 min of reperfusion.[18] IL-6 was reported to be a marker rather than a critical tissue mediator of inflammation.[19] The cytokine tumor necrosis factor-α (TNF-α) also actively contributes to depressed myocardial performance after CPB.[20] Recent data allow us to better understand these effects, TNF-α and interleukin-1β synergetically depress human myocardial contractile function through a mechanism mediated by sphingosine.[21] Sphingosine is rapidly released after the exposure of cardiac myocytes to TNF-α and it exerts a negative inotropic effect impeding Ca^{+2} induced Ca^{+2} release from sarcoplasmic reticulum. TNF-α also stimulates NF-$_k$B production through this mechanism mediated by sphingosine.

Corticosteroids have also long been used to reduce inflammation and anti-inflammatory effects of steroids have been demonstrated following CPB.[22] A significant reduction of pro-inflammatory cytokines has been observed after pretreatment with methylprednisolone in patients undergoing CPB.[23,24] Steroid pretreatment also decreases endotoxin release and leukocytes' integrin expression.[25] It was also recently reported that high dose of glucocorticoids reduced ischemia-reperfusion induced apoptosis in immature piglet hearts. The reduction of neutrophile adhe-

sion and activation proteins in neonatal myocardium was associated with less apoptotic cell death after glucocorticoid administration. The blunting of apoptosis in glucocorticoid-treated animals was also associated with improved recovery of left ventricular systolic function in neonatal animals after CPB and circulatory arrest.[26] However, large doses of steroids can cause abnormal metabolic responses such as metabolic acidosis and hyperglycemia. Thus, the efficacy of lower doses of methylprednisolone (5 and 10 mg/kg) to attenuate systemic inflammatory reaction with a lower risk of generating an abnormal metabolic response, was tested recently. Bourbon et al demonstrated that low-dose methylprednisolene could inhibit SIR by quantifying proinflammatory cytokines (TNF-a and IL-6), and free radical generation by polymorphonuclear leucocytes throughout CPB.[27]

A number of serum biochemical markers for myocardial injury during and after CPB were identified.[28] Creatine kinase (CK)-MB heart-specific isoform was reported to peak within 6-8 hour after surgery, and to decrease to normal values within 2-3 days. Postoperative cTn levels can be used easily and confidently to measure the degree of myocardial ischemia-reperfusion injury occurring during CPB. Cardiac troponins T and I isoforms were strongly associated with myocardial injury (up to 50-fold increase within 2 hour after regional ischemia). The duration of troponin I elevation is typically 5 days but there is variation depending on infarct size.

In this present study, acute cardioprotective effect of corticosteroids during CPB was tested by using cardiac marker measurement. cTnI levels were significantly higher at 2 hours after CPB (p= 0.015), at 6 hours of reperfusion (p= 0.049) and at postoperative day 5 in group I (p= 0.0001). Furthermore, the amount of troponin relase due to ischemia-reperfusion injury occurring during CPB calculated as the differences between T1 and T0 was also significantly lower in group I when compared with group II. Checchia et al reported similar findings such that dexamethasone administration before CPB in children resulted in a significant decrease in cTnI levels at 24 hours postoperatively.[29] Moreover, previous studies demonstrated that perioperative measurement of cTnI reflects myocardial damage and systemic inflammatory response and allows an improved peri- and postoperative management.[30]

As there is still controversy on the main mechanism of myocardial cell injury during CPB, more extensive clinical investigation is necessary to explain the mechanism-ischemic cardiac arrest during aortic cross-clamp or systemic inflammatory response secondary to CPB-that plays a pivotal role in myocardial ischemia-reperfusion injury. A recently reported study compares the early clinical outcomes and inflammatory response of patients undergoing elective on-pump beating heart coronary artery bypass grafting.[31] This study provided the opportunity to examine the isolated effect of CPB and served to eliminate the effects of global myocardial ischemic arrest using aortic cross-clamping and cardioplegic arrest. This study showed that there was significant elevation in the levels of interleukin-6, interleukin-8, interleukin-10 and TNF-α during and immediately after the operations in the on-pump beating heart group when compared with the off-pump group. However, this study compared only the patients who underwent off-pump beating and on-pump beating myocardial revascularization and the patients with aortic cross-clamp and cardioplegic arrest were not included. Therefore, this study could not clarify the mechanism-cardioplegic arrest or systemic inflammatory response secondary to CPB- that plays a pivotal role in myocardial injury during CPB. However, regardless of the pivotal mechanism of myocardial cell injury during CPB, any strategy that reduces systemic inflammatory response can theoretically minimize the morbidities associated with coronary artery surgery with CPB. Therefore, we believe that corticosteroids may be the answer.

In conclusion, in the future, the acute protective effect of corticosteroids will be used more extensively to limit ischemia-reperfusion injury in the myocardium and other organs occurring during conventional aortocoronary bypass graft surgery with CPB when it will be inevitable.

REFERENCES

1. Libby, Marko PR, Bloor CM, Sobel BE, Braunward E. Reduction of experimental myocardial infarct size by corticosteroid administration. J Clin Invast 1973;52:599-607.
2. Spath JA, Lane DL, Lefer AM. Protective action of methylprednisolone on the myocardium during experimental myocrdial ischemia in the cat. Circ Res 1974;35:44-51.
3. Sholter DE, Armstrong PW. Adverse efects of corticosteroids on the cardiovascular system. Can J Cardiol 2000;16:505-11.
4. Katus HA, Remppis A, Looser S, Hallermeyer K, Scheffold T, Kubler W. Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in patients. J Mol Cell Cerdiol 1989;21:1349-53.
5. Bodor GS, Porter S, Landt S, Ledenson JH. Development of monoclonal antibodies for an assay of cardiac troponin-I and preliminary in suspected casese of myocardial infarction. Clin Chem 1992;38:2203-14.
6. Katus HA, Loser S, Hallermayer K, et al. Development and in vitro characterization of a new immunoassay of cardiac troponin T. Clin Chem 1992;38:386-93.
7. Mair J, Wieser CH, Seibt I, et al. Troponin T to diagnose myocardial infarction in bypass surgery. Lancet 1991;337:334-5.
8. Hafezi-Moghadam A, Simoncini T, Yang E, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. Nat Med 2002;8:473-9.
9. Becmer PB, Gloss B, Schmid W, Strahle U, Schultz G. In vivo protein- DNA interactions in a glucocorticoid response element require the presence of the hormone. Nature 1986;324:686-8.
10. Loscalso J. Nitric oxide and vascular disease. N Eng J Med 1995;333:251-3.
11. De Caterina R, Libby P, Peng HB, et al. Nitric oxide decreases cytokine-induced activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules proinflammatory cytokines. J Clin Invest 1995;96:60-8.
12. Thiemermann C. Corticosteroids and cardioprotection. Nat Med 2002;8:453-5.
13. La M, Tailor A, D'Amico M, Flower RJ, Perretti M. Analysis of the protection afforded by annexin 1 in ischaemia-reperfusion injury: Focus on neutrophil recruitment. Eur J Pharmacol 2001;429:263-78.
14. La M, D'Amico M, Bandiera S, et al. Annexin 1 peptides protect against experimental myocardial ischemia-reperfusion: Analysis of their mechanism of action. FASAB J 2001;15:2247-56.
15. Anselmi A, Abbate A, Girola F, et al. Myocardial ischemia, stunning, inflammation and apoptosis during cardiac surgery: A review of evidence Eur J Cardiothorac Surg 2004;25:304-11.
16. Bolli R, Marba'n E. Molecular and cellular mechanisms of myocardial stunning. Physiol Rev 1999;79: 609-34.
17. Kilger E, Weis F, Briegel J, et al. Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery. Crit Care Med 2003;31:1068-74.
18. Zahler S, Massoudy P, Heartly H, Hahnel C, Meisner H, Becker BF. Acute cardiac inflammatory responses to postischemic reperfusion during cardiopulmonary bypass. Cardiovasc Res 1999;41:722-30.
19. Wan S, Yim A. Cytokines in myocardial injury: Impact on cardiac surgical approach. Eur J Cardiothorac Surg 1999;16:S107-11.
20. te Velthius H, Jansen PG, Oudemans-van Straaten HM, Sturk A, Eijsman L, Wildevuur CR. Myocardial performanca in elderly patients after cardiopulmonary bypass is suppressed by tumor necrosis factor. J Thorac Cardiovasc Surg 1995;110:1663-9.
21. Cain BS, Meldrum DR, Dinarello CA. Tumor necrosis factor-alpha and interleukin-1beta synergistically depress human myocardial function. Crit Care Med 1999;27:1309-18.
22. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232-44.
23. Kawamura T, Inada K, Nara N, Wakusawa R, Endo S. Influence of methylprednisoloneon cytokine balance during cardiac surgery. Crit Care Med 1999;27:545-8.
24. Celik JB, Gormus N, Okesli S, Gormus ZI, Solak H. Methylprednisolone prevents inflammatory reaction occurring during cardiopulmonary bypass: Effects on TNF-alpha, IL-6, IL-8, IL-10. Perfusion 2004;19:185-91.
25. Wan S, LeClere JL, Huynh CH, et al. Does steroid pretreatment increase endotoxin release during clinical cardiopulmonary bypass? J Thoroc Cardiovasc Surg 1999;117:1004-8.
26. Pearl JM, Nelson DP, Schwartz SM, et al. Glucocorticoids reduce ischemia-reperfusion-induced myocardial apoptosis in immature hearts. Ann Thorac Surg 2002;74:830-6.

27. Bourbon A, Vionnet M, Leprince P, et al. The effect of methylprednisolone treatment on the cardiopulmonary bypass induced systemic inflammatory response. Eur J Cardiothorac Surg 2004;26:932-8.
28. Birdi I, Angelini GD, Bryan AJ. Biochemical marker of myocardial injury during cardiac operation. Ann Thorac Surg 1997;63:879-84.
29. Checchia PA, Backer CL, Bronicki RA, et al. Dexamethasone reduces postoperative troponin levels in children undergoing cardiopulmonary bypass. Crit Care Med 2003;31:1742-5.
30. Hammer S, Loeff M, Reichenspurner H, et al. Effect of cardiopulmonary bypass on myocardial function, damage and inflammation after cardiac surgery in newborns and children. Thorac Cardiovasc Surg 2001; 49: 349-54.
31. Innes YPW, Ahmed AA, Song W, et al. Beating heart revascularization with or without cardiopulmonary bypass. Evaluation of inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg 2004;127: 1624-31.