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Pretreatment with Methylprednisolone Improves Myocardial Protection during On-Pump Coronary Artery Bypass Surgery

Dr. Demir

Tolga Demir, MD,[1] Mehmet Umit Ergenoglu, MD,[1] Hale Bolgi Demir, MD,[2] Nursen Tanrikulu, MD,[3] Mazlum Sahin, MD,[4] Emre Gok, MD,[4] Kubilay Korkut, MD,[1] Ergun Demirsoy, MD, PhD[1]

Departments of [1]Cardiovascular Surgery and [3]Anesthesiology, Kolan International Hospital; [2]Department of Cardiovascular Surgery, Medicana International Hospital; [4]Department of Cardiovascular Surgery, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

ABSTRACT

Background: This study was undertaken to determine whether methylprednisolone could improve myocardial protection by altering the cytokine profile toward an anti-inflammatory course in patients undergoing elective coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB).

Methods: Forty patients who were scheduled for elective CABG surgery were randomized into two groups: the study group (n = 20), who received 1 g of methylprednisolone intravenously before CPB, and the control group (n = 20), who underwent a standard CABG surgery without any additional medication. Blood samples were withdrawn prior to surgery (T1) and then 4 hours (T2), 24 hours (T3), and 36 hours (T4) after CPB. Plasma levels of interleukin (IL)-6, IL-10, creatine kinase isoenzyme MB (CK-MB), cardiac troponin-t (cTnT), and blood glucose as well as neutrophil counts were measured at each sampling time.

Results: A comparison of patients between both groups revealed significantly high levels of IL-6 in the control group at T2, T3, and T4 with respect to T1 (T2: $P < .001$; T3: $P < .001$; T4: $P < .001$). IL-10 levels were significantly higher in the study group at T2 compared with the control group ($P = .007$). CK-MB levels were significantly lower in the study group than in the control group at T4 ($P = .001$). The increase of cTnT was higher in the control group at T3 and T4 compared with the study group (T3: $P = .002$; T4: $P = .001$).

Conclusions: This study demonstrates that methylprednisolone is effective for ensuring better myocardial protection during cardiac surgery by suppressing the inflammatory response via decreasing the levels of IL-6 and by increasing anti-inflammatory activity through IL-10.

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Correspondence: Tolga Demir, MD, Kaptanpasa Mah, Darulaceza Cad, No: 14, 34384, Okmeydani, Istanbul, Turkey; +90-532-749-1319; fax: +90-212-855-75-70 (e-mail: dr.tolgademir@gmail.com).

INTRODUCTION

Despite recent advances in surgical techniques and perfusion methods in cardiac surgery, the systemic inflammatory response after cardiopulmonary bypass (CPB) continues to be a significant cause of morbidity and an occasional cause of mortality [Turkoz 2001]. Nonspecific activators of the inflammatory response include surgical trauma, transfusion, and hypothermia. In addition, CPB may specifically activate the inflammatory response via contact activation of the immune system following the exposure of blood to the foreign surfaces of the CPB circuit and ischemia-reperfusion injury due to aortic cross-clamping [Laffey 2002]. Several studies have shown that this response involves complement activation, neutrophil degranulation, and free radical production, together with cytokine release, leading to an increase in capillary permeability, the accumulation of interstitial fluid, and organ dysfunction [Ashraf 1998].

Cytokines have a multitude of biological consequences, ranging from minor target organ dysfunction to multi-organ failure [Wei 2001]. Their release can be stimulated by a number of factors, including ischemia-reperfusion, complement activation, and the effect of other cytokines. Interleukin (IL)-6, a pro-inflammatory cytokine released by cells, such as endothelial cells, monocytes, and T cells, is a relevant mediator of organ dysfunction based on its major role of recruitment and activation of leukocytes. Experiments have shown that IL-6 is released during reperfusion of the ischemic myocardium [Lango 2001]. IL-10 is a potent anti-inflammatory cytokine that reduces neutrophil adhesion to activated endothelial cells [Volk 2003]. The maintenance of normal postoperative organ function and prognosis following CPB is likely to depend on the balance between pro-inflammatory and anti-inflammatory cytokine synthesis [Laffey 2002; Hovels-Gurich 2002].

Numerous studies have demonstrated that pro-inflammatory cytokines contribute to postoperative myocardial ischemia, segmental wall motion abnormalities, and even hemodynamic instability after CPB [Gulielmos 2000]. Cardiac troponin-t (cTnT) and creatine kinase isoenzyme MB (CK-MB) are reliable markers for the diagnosis of myocardial cell necrosis and for estimating the severity of myocardial damage [Tunerir 1999].

The development of strategies to control the inflammatory response following cardiac surgery is currently the focus of considerable research effort. Many approaches have been examined in various clinical studies, including the use of corticosteroids, the use of aprotinin, improvement of the biocompatibility of CPB circuits, and minimization of exposure to the CPB circuit.

Corticosteroids have widespread and potent anti-inflammatory properties that are often beneficial for the treatment of acute inflammatory disease. These drugs reduce early inflammatory processes, such as increased capillary permeability, edema formation, and leukocyte migration. Their anti-inflammatory effects are related to the suppression of the stimulus-dependent expression of many pro-inflammatory proteins through the inhibition of transcriptional cascades in target cells [Rubens 2005]. However, the use of corticosteroids in the context of CPB continues to be controversial because of their potential risks. Further investigations are needed to understand the mechanisms by which corticosteroids alter the inflammatory response and the levels of corticosteroids that induce the maximal suppression of inflammation.

Therefore, this study was undertaken to determine whether steroids could improve myocardial protection by altering the cytokine profile toward an anti-inflammatory course in patients undergoing elective coronary artery bypass graft surgery (CABG) with CPB.

MATERIALS AND METHODS

Patients

This clinical trial was approved by the local ethics committee of Istanbul University. Informed consent was obtained before participation from eligible patients who were scheduled for CABG with CPB. Exclusion criteria were emergency surgery, previous heart surgery, other cardiac procedures in addition to CABG, renal or hepatic dysfunction, immunological or coagulation disorders, infection during the week preceding surgery, pre-operative use of antibiotics or corticosteroids, history of recent peptic ulcer disease, diabetics on insulin therapy, and white blood cell count over 11,000 mm^{-3}.

Each patient was randomized to receive either 1 g intravenous methylprednisolone (study group; n = 20) or similar volumes of intravenous isotonic sodium chloride solution (control group; n = 20) just at the beginning of CPB.

Anesthesia Protocol

The intraoperative anesthetic technique was standardized and consisted of intravenous fentanyl (15 µg/kg), midazolam (0.1 mg/kg), and vecuronium (0.1 mg/kg). A single lumen endotracheal tube was inserted, and isoflurane was used to maintain anesthesia in a clinically related concentration. After harvesting the internal mammary artery (IMA), 300 IU/kg heparin was given intravenously in all cases. Further doses were administered if necessary to maintain an activated clotting time of more than 450 seconds. Invasive arterial pressure, central venous pressure, and 6-led ECG monitoring were performed during the procedure.

Cardiopulmonary Bypass Technique

The extracorporeal circuit consisted of a hollow-fiber membrane oxygenator (D708 Simplex III, Dideco, Mirandola, Italy) with an integrated cardiotomy filter, an extracorporeal circuit line set, and a roller pump. The circuit was primed with 1500 mL of Ringer's lactate solution, 250 mL of mannitol, and packed red blood cells to obtain a hematocrit value of the circulating volume of approximately 25%. Nonpulsatile extracorporeal circulation was initiated at flows of 2.4 to 2.6 $L \cdot min^{-1} \cdot m^{-2}$. Moderate systemic hypothermia (32° to 34°C) was used. After aortic cross-clamping, cardiac arrest was achieved by the antegrade infusion of 1.0 L of cold crystalloid cardioplegic solution (Plegisol, Abbott Laboratories, Chicago, IL, USA). Myocardial protection was achieved with 10 mL/kg cold blood cardioplegia given every 20 minutes. All distal anastomoses were performed, the cross-clamp was removed, and the proximal anastomoses to the aorta were completed during the rewarming period. Extracorporeal circulation was terminated at a nasopharyngeal temperature of 37°C. Heparin was neutralized by an intravenous drip-infusion of 300 IU/kg of protamine sulfate within 5 minutes after the end of CPB.

Cytokine and Biochemical Measurements

Blood samples were withdrawn prior to skin incision (T1), 4 hours after CPB (T2), 24 hours after CPB (T3), and 36 hours after CPB (T4). Samples were immediately cooled to 4°C and centrifuged at 4500 rpm for 10 minutes. Plasma was stored at -40°C until it was used for the assays. The levels of IL-6 and IL-10 were measured by enzyme-linked immunosorbent assay kits (BioSource International, USA) according to the manufacturer's instructions. The limit of sensitivity of each assay, as defined by the manufacturer, is 2 pg/mL. In addition, plasma levels of the CK-MB and cTnT and the neutrophil counts were also measured at each sampling time.

Statistical Analysis

Fisher's exact test was applied to categorical data. Student's *t* test (or Mann-Whitney *U* test, where appropriate) was used to test the difference between means in two groups

Table 1. Patient Demographics*

	Study Group (n = 20)	Control Group (n = 20)	*P*
Age, y	62.95 ± 8.97	65.20 ± 9.42	.44
Male / female, n	12 / 8	13 / 7	.74
Weight, kg	71.25 ± 9.55	69.75 ± 7.35	.58
Height, cm	164.45 ± 8.36	163.95 ± 7.87	.84
Smoking, n	7	10	.35
Type II DM, n	7	6	.74
EF, %	47.35 ± 11.79	46.20 ± 11.71	.76

*Data are presented as the mean ± SD where indicated. DM indicates diabetes mellitus; EF, ejection fraction.

Table 2. Operative Parameters of the Patients*

	Study Group (n = 20)	Control Group (n = 20)	*P*
CPB time, min	115.40 ± 31.87	123.20 ± 36.20	.47
Aortic cross-clamp time, min	67.60 ± 18.94	71.80 ± 19.81	.50
Lowest temperature, °C	32.54 ± 1.47	32.29 ± 1.37	.59
MAP during aortic cross-clamping, mmHg	66.90 ± 6.55	65.60 ± 6.27	.53
Lowest hematocrit level during CPB, %	26.73 ± 3.88	25.73 ± 3.35	.39
Number of distal anastomoses	3.30 ± 1.08	3.35 ± 1.03	.88

*Data are presented as the mean ± SD where indicated. CPB indicates cardiopulmonary bypass; MAP, mean arterial pressure.

Table 3. Postoperative Data*

	Study Group (n = 20)	Control Group (n = 20)	*P*
Dopamine dosage, mg/kg	2.37 ± 4.81	3.41 ± 4.97	.55
Dobutamine dosage, mg/kg	2.41 ± 5.63	4.86 ± 7.61	.35
Adrenaline dosage, mg/kg	0.01 ± 0.03	0.06 ± 0.15	.55
Duration on MV, hours	8.67 ± 3.08	8.02 ± 3.81	.49
Surgical infection, n	0	0	1.00
Stay in ICU, days	2.20 ± 0.41	2.45 ± 0.68	.37
Stay in hospital, days	8.25 ± 1.83	9.35 ± 2.39	.11

*Data are presented as the mean ± SD where indicated. ICU indicates intensive care unit; MV, mechanical ventilation.

regarding the demographic and clinical characteristics of the patients and the appropriate perioperative data. Time-dependent variations of biological variables were analyzed by the Wilcoxon test, and intergroup comparison at specific sample times were analyzed by Mann-Whitney *U* test. A *P* value less than .05 was considered significant. If a significant difference was found, the exact *P* value was given. If no significance was found, the term n.s. (not significant) was given. The results were expressed as the mean ± standard error of the mean unless otherwise indicated.

RESULTS

Clinical Outcome

Twenty patients were randomized to each group. The demographic and clinical characteristics and intraoperative data are presented in Tables 1, 2, and 3, respectively. No significant differences were observed between the two groups. Complete revascularization was achieved in all patients. The periods for weaning off of the mechanical ventilators were similar, and no

Table 4. Differences in Neutrophil Levels between the Control Group and the Study Group*

Time Point	Control Group (n = 20)	Study Group (n = 20)	*P*
T1	4.50 ± 1.84	4.65 ± 1.46	.71
T2	9.47 ± 3.97	13.22 ± 3.18	.001
T3	9.44 ± 4.04	11.99 ± 2.64	.006
T4	10.19 ± 2.24	13.23 ± 2.97	.001

*Data are presented as the mean ± SD where indicated. T1 indicates prior to skin incision; T2, 4 hours after CPB; T3, 24 hours after CPB; T4, 36 hours after CPB.

Table 5. Differences in Blood Glucose Levels between the Control Group and the Study Group*

Time Point	Control Group (n = 20)	Study Group (n = 20)	*P*
T1	108.75 ± 22.92	102.30 ± 29.75	.20
T2	164.35 ± 46.49	200.05 ± 44.86	.02
T3	190.05 ± 66.32	248.10 ± 77.26	.02
T4	175.95 ± 62.40	185.15 ± 62.61	.55

*Data are presented as the mean ± SD where indicated. T1 indicates prior to skin incision; T2, 4 hours after CPB; T3, 24 hours after CPB; T4, 36 hours after CPB.

significant difference in the length of intensive care unit or hospital stay was observed between groups. No patient required exploration for postoperative bleeding, and there were no operative deaths or important adverse complications.

Total postoperative blood loss into the chest drains was similar in both groups: 783.54 mL (range, 1350 to 200 mL) in the study group versus 850.33 mL (range, 1200 to 150 mL) in the control group. The inotropic agents were used according to the hemodynamic status of the patients and the values in Table 3 represents their average usage in each group. No statistically significant difference was found between the groups in terms of their need for inotropic agents.

Inflammatory Response

In the study group, the plasma concentrations of IL-6 were significantly higher than their normal range at T2, T3, and T4 ($P < .001$). IL-10 levels were also elevated above their normal ranges at T2, T3, and T4 ($P < .001$).

In the control group, similar results were obtained, and the IL-6 and IL-10 levels were significantly elevated above their normal ranges at T2, T3, and T4 (IL-6: $P < .001$; IL-10: $P < .001$).

A comparison between both groups revealed statistically significant lower levels of IL-6 in the study group compared with the control group at T2, T3, and T4 ($P < .001$; Figure 1, A).

The plasma concentration of IL-10 between both groups revealed significantly higher levels in the study group than

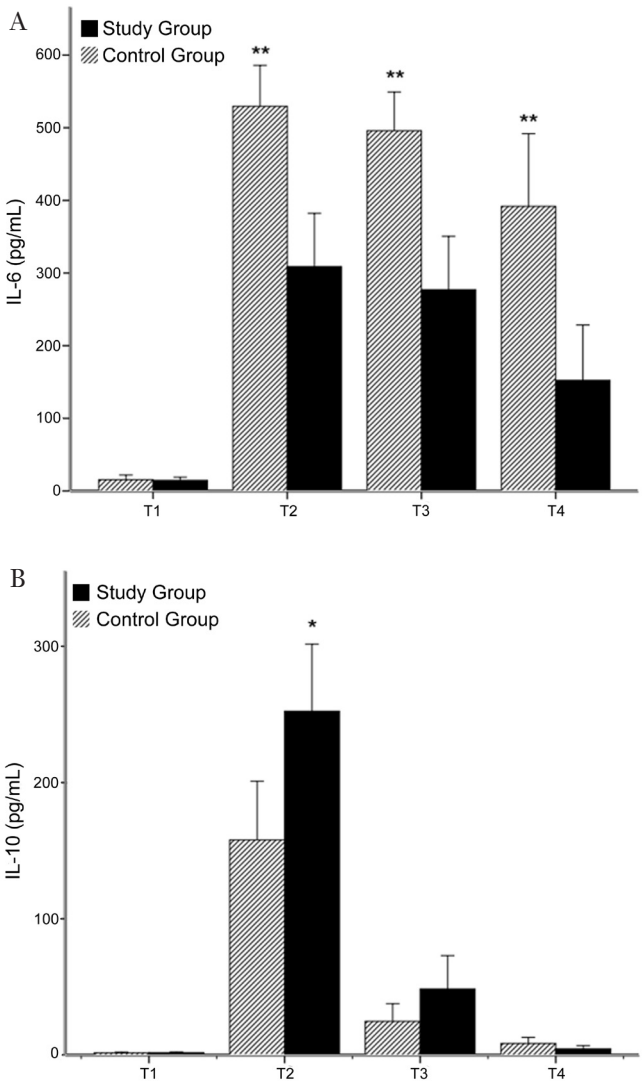

Figure 1. (A) Plasma concentrations (mean ± SD) of interleukin (IL)-6; and (B) IL-10 in the control (n = 20) and study (n = 20) groups at 4 time points. Statistically significant differences between the groups: *P < .05 and **P < .001.

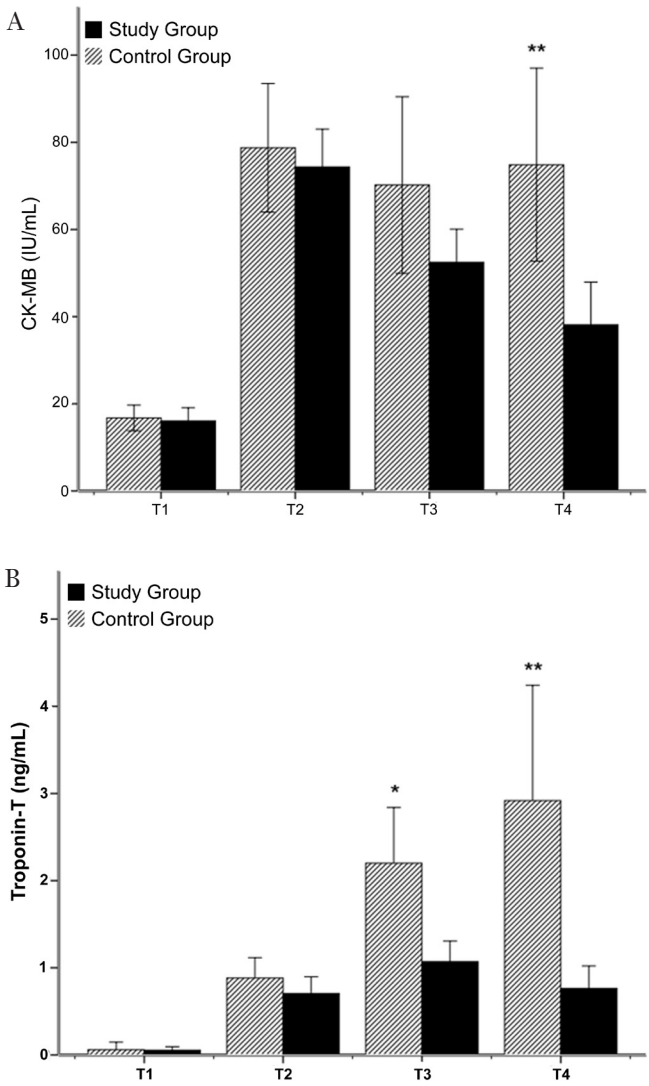

Figure 2. (A) Plasma concentrations (mean ± SD) of creatine kinase isoenzyme MB (CK-MB); and (B) cardiac troponin-t in the control (n = 20) and study (n = 20) groups at 4 time points. Statistically significant differences between the groups: *P < .05 and **P < .001.

the control group at T2 (P = .007). There were no statistically significant differences in the IL-10 levels between both groups at T1, T3, and T4 (Figure 1, B).

Neutrophil levels were significantly higher in the study group than in the control group at T2, T3, and T4 (T2: P = .001; T3: P = .006; T4: P = .001; Table 4).

Biochemical Parameters

A comparison of CK-MB levels within the study group revealed significantly higher levels at T2, T3, and T4 than at T1 (P < .001). However, the CK-MB levels decreased progressively after T2. CK-MB levels were lower at T3 and T4 than at T2, while they were still higher than at T1. A comparison of the CK-MB levels within the control group revealed higher levels at T2, T3, and T4 than at T1, and the highest level was observed at T4 (P < .001).

A comparison of the CK-MB levels between the two groups revealed significantly lower levels in the study group at T4 (P = .001; Figure 2, A).

A comparison of the troponin-t levels revealed significantly higher levels at T2, T3, and T4 compared to T1 within both groups. However, in the study group, the troponin-t levels at T4 decreased significantly compared with T3 (P = .006). A comparison of the troponin-t levels between the two groups revealed significantly higher levels at T3 and T4 in the control group than in the study group (T3: P = .002; T4: P = .001; Figure 2, B).

A comparison of the blood glucose levels between the two groups revealed significantly higher levels at T2 and T3 in the study group (T2: P = .02; T3: P = .02; Table 5).

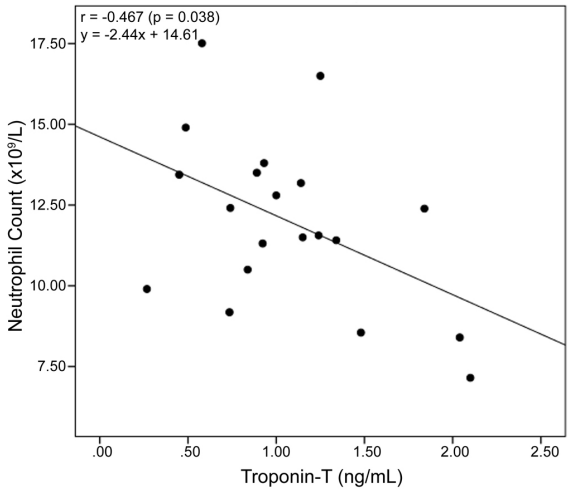

Figure 3. The regression analysis revealed a significant negative correlation between the neutrophil count and the cardiac troponin-t levels at T3 in the study group.

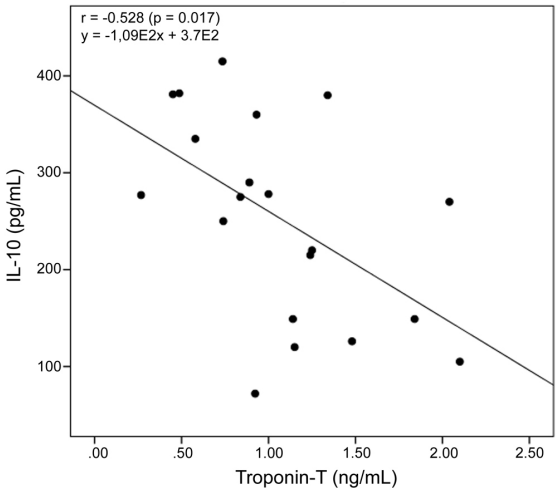

Figure 4. The regression analysis revealed a significant negative correlation between the interleukin (IL)-10 levels at T2 and the troponin-t levels at T3 in the study group.

In the study group, a significant negative correlation was observed between the neutrophil count and the troponin-t levels at T3 (r = 0.467, *P* = .038; Figure 3). In the same group, a significant negative correlation was also observed between the IL-10 levels at T2 and the troponin-t levels at T3 (r = 0.528, *P* = .017; Figure 4).

DISCUSSION

A systemic inflammatory response due to extracorporeal circulation in cardiac surgery may lead to postoperative early complications, including multi-organ failure and even death [Wan 1999]. Several methods have been previously utilized to reduce inflammation after cardiac surgery. These methods included substituting the internal surface of the cardiopulmonary bypass device with different materials, cardiac surgery without extracorporeal circulation, and the addition of pharmacological agents such as aprotinin; corticosteroids; inhibitors of complement system; and anti-mediator agents [Bergseth 2011; Jansen 1996; Harig 1999]. The presence of inflammation and the effectiveness of the method in reducing the inflammation should both be demonstrated. While previous studies have utilized biochemical and pathological analyses of tissues to demonstrate inflammation, the blood levels of the cytokines that are responsible for inflammatory response were used for the same purpose in the present study.

Methylprednisolone has been used in cardiac surgery for 30 years [Wan 1997]. Previously, it was used to prevent low cardiac output after cardiopulmonary bypass; however, methylprednisolone is currently used to reduce the anti-inflammatory affect [Tassani 200]. Methylprednisolone reduces the systemic inflammatory response after cardiopulmonary bypass via altering the levels of pro-inflammatory and anti-inflammatory cytokines.

Cytokines are agents that are associated with inflammation and are released from several cells, including activated lymphocytes, tissue macrophages, and monocytes. They are divided into pro-inflammatory and anti-inflammatory cytokines according to their function. IL-6 is a pro-inflammatory cytokine that reaches a maximum at the 4th hour of cardiopulmonary bypass and is responsible for fever and increased vascular permeability [Ferroni 1998; Butler 1993]. The increase in the levels of IL-6 is associated with the duration of cardiopulmonary bypass [Wan 1999]. IL-10 is a cytokine with anti-inflammatory activity and is secreted from macrophages to suppress the inflammatory response. IL-10 prevents the synthesis of pro-inflammatory cytokines. Blood levels of IL-10 reach a maximum after the establishment of cardiopulmonary bypass.

This experimental study was undertaken to demonstrate the effect of methylprednisolone on inflammation after cardiopulmonary bypass, and the level of myocardial injury by measuring the blood cytokine levels and performing a biochemical analysis of the enzymes released after tissue damage. The level of the inflammatory response and the level of myocardial injury were evaluated by measuring the blood IL-6 and IL-10 levels.

In our study, the significantly lower levels of IL-6 at the 4th, 24th, and 36th hours after the establishment of CPB in patients who received 1 g of methylprednisolone before CPB indicate the effectiveness of methylprednisolone in suppressing the pro-inflammatory cytokines. The levels of IL-10 at 4 hours after cardiopulmonary bypass were significantly higher in the study group than in the control group. This finding is concordant with the anti-inflammatory characteristics of IL-10, which was induced by methylprednisolone. However, the IL-10 levels were lower at 36 hours after cardiopulmonary bypass in the study group than in the control group. The relatively higher levels of IL-10 in the control group at

36 hours after cardiopulmonary bypass is likely a physiological response to suppress the ongoing higher levels of IL-6 in the control group.

In agreement with previous studies on the anti-inflammatory characteristics of methylprednisolone in cardiac surgery, we also conclude that methylprednisolone is effective in suppressing the inflammatory response after cardiopulmonary bypass [Tassani 2000; Giomarelli 2003; Rasmussen 2002].

Hemodynamic measurements and biochemical analyses may be performed to detect the myocardial injury induced by inflammation. While hemodynamic measurements demonstrate functional injury, biochemical analyses demonstrate cellular injury of the myocardium. Biochemical analyses of cardiac troponin-t and CK-MB is used for this purpose. In our study, myocardial injury was evaluated by measuring CK-MB and troponin-t. Our study revealed that the CK-MB levels at the 36th hour and the troponin-t levels at the 24th and 36th hours after the establishment of cardiopulmonary bypass were significantly lower in patients who received methylprednisolone therapy than in the control group. This finding demonstrates that suppressing the inflammatory response with methylprednisolone in patients undergoing cardiac surgery with cardiopulmonary bypass reduces the myocardial injury induced by the inflammatory response.

Neutrophils migrate to the inflammation zone, and this step may be blocked with corticosteroids. In our study, the neutrophil count was significantly higher in the study group, which was in concordance with the blockage of neutrophil migration from the vessels.

The most common metabolic side effect of corticosteroids is hyperglycemia. Previous studies also demonstrated a significant increase in the blood glucose levels after the administration of methylprednisolone. In our study, we also detected higher glucose levels in patients who received methylprednisolone therapy. However, by the 36th hour after cardiopulmonary bypass, the difference between both groups was not significant.

The preoperative administration of methylprednisolone suppresses the inflammatory response by decreasing the levels of IL-6 and increasing the levels of IL-10. These alterations in the cytokine profile improve myocardial protection. Postoperative myocardial ischemia and segmental wall motion abnormalities are associated with the elevation of interleukin-6 levels [Hennein 1994]. Steroid administration before CPB is associated with a significant reduction of postoperative cTnT and increased myocardial protection [Heying 2012]. The results that we obtained in this study are concordant with the previous studies investigating the effects of methylprednisolone during cardiac surgery using cardiopulmonary bypass.

It was previously suggested that methylprednisolone should be administered at least one hour prior to cardiopulmonary bypass for better myocardial protection [Tassani 2000]. The poor results of a previous study (Chaney et al) were possibly due to higher doses of methylprednisolone (2 × 30 mg/kg) than the dose used in our study (1 × 1 g) or used in the one performed by Tassani et al [Chaney 2001; Tassani 1999]. High doses of methylprednisolone increase the pulmonary side effects and may result in prolonged periods of mechanical ventilation with decreased lung compliance. For this reason, the methylprednisolone dose for adults is suggested to be less than 1 g [Tassani 2000; Giomarelli 2003].

The primary limitation of this study is the small number of patients analyzed; the results could have been more conclusive if a larger sample was analyzed. Moreover, high-dose prophylactic corticosteroid administration before cardiopulmonary bypass remains controversial, as no trials are available that have been sufficiently powered to draw conclusions on their effect on major clinical outcomes.

Despite its limitations, this randomized clinical study concludes that one gram of methylprednisolone administered prior to cardiopulmonary bypass generates significant anti-inflammatory activity by altering the balance between pro-inflammatory and anti-inflammatory cytokines, and this anti-inflammatory activity improves myocardial protection by suppressing the inflammation induced by cardiopulmonary bypass. Further well-designed and adequately powered randomized controlled trials are needed to more accurately estimate the benefit and harm of the use of prophylactic steroids in patients undergoing cardiac surgery to reduce postoperative myocardial injury.

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