The Effect of Continuous Low Dose Methylprednisolone Infusion on Inflammatory Parameters in Patients Undergoing Coronary Artery Bypass Graft Surgery: a Randomized-Controlled Clinical Trial

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Abstract- This trial was performed to determine if a continuous low-dose infusion of methylprednisolone is as effective as its bolus of high-dose in reducing inflammatory response. The study was single-center, double-blinded randomized clinical trial and performed in a surgical intensive care unit of an academic hospital. In this study, 72 consecutive patients undergoing elective coronary artery bypass grafting (CABG) were assigned to receive either a methylprednisolone loading dose (1mg/kg) followed by continuous infusion (2mg/Kg/24 hours for 1 day) (low-dose regime) or a single dose of methylprednisolone (15 mg/kg) before cardiopulmonary bypass (high dose regime). Serum concentrations of IL-6 and C- reactive protein (CRP) were measured preoperatively and 6, 24 and 48 hours after surgery, and serum creatinine was measured before the operation and 24, 48 and 72 hours postoperatively. The measurements were then compared between the groups to evaluate the efficacy of each regimen. The basic characteristics and measurements were not different between the study groups. There was no significant difference in IL-6 and CRP elevation (P=0.52 and P=0.46, respectively). Early outcomes such as the length of stay in the intensive care unit, intubation time, changes in serum creatinine and blood glucose levels, inotropic support, insulin requirements, and rate of infection were also similar in both groups. A continuous low dose infusion of methylprednisolone was as effective as a single high dose methylprednisolone in reducing the inflammatory response after CABG with extracorporeal circulation with no significant difference in the postoperative measurements and outcomes.

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Introduction

Cardiopulmonary bypass (CPB) and surgical trauma during cardiac surgery trigger a systemic inflammatory response, manifested by cardiovascular and pulmonary dysfunction (1-3). As a result, major postoperative morbidities such as renal and hepatic dysfunction, respiratory failure, neurologic alterations, bleeding disorders, arrhythmia and fulminant multiple organ failure may occur (4). Inflammatory markers which play major role in the inflammatory response (5), such as C-reactive protein (CRP), tumor necrosis factor, interleukin-6 (IL-6), and IL-8 rise within hours and remain elevated for the first few days after cardiac surgery (6).

Different drugs and several measures have been proposed to attenuate postoperative inflammation (7-9). Corticosteroids with their multi inhibitory effects on various components of the inflammatory response have remained potent and preferred anti-inflammatory agents (10). They can prevent hemodynamic instability after CPB, inhibit the activity of the leukocyte and tissue

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plasminogen activator and reduce detectable plasma pro-inflammatory cytokines (11-12). Methylprednisolone not only can induce down-regulation of systemic inflammation, significantly improves the pulmonary and extra pulmonary organ dysfunction and reduces the duration of mechanical ventilation, but also can reduce the occurrence of atrial fibrillation and the length of stay in the intensive care unit (ICU) (13-14).

Studies comparing the effect of corticosteroids on the post-CPB inflammatory response have yielded different results (11-12). Corticosteroids can prevent hemodynamic instability after CPB and improve the postoperative course by reducing hyperthermia, hypotension, and intravenous fluid requirements as well as optimizing urine output (2,15-16). A high dose of corticosteroids can cause several complications, such as immunosuppression, hyperglycemia, and increased rate of infection while low doses are expected to be ineffective (1).

Aim of this study was to compare the efficacy of a continuous low-dose infusion of methylprednisolone and a high-dose bolus in reducing the production of pre-inflammatory factors as well as the effect on the early outcomes in patients undergoing CABG.

Materials and Methods

Participants and materials

A total of 72 consecutive patients undergoing CABG were enrolled in this double-blinded controlled randomized trial between November 2010 and November 2011. The exclusion criteria consisted of age <18 years, uncontrolled diabetes mellitus (blood glucose >180mg/dl), renal failure (serum creatinine>2mg/dl), hepatic failure (transaminases>40 IU/L), confirmed evidence of a recent fungal or bacterial infection (<2 weeks), allergic to corticosteroids, and recent corticosteroids use (<4 weeks). The Patients were then randomized to intervention and control groups according to computer-generated block randomisation table.

The Ethics Committee and Research Board of Tehran Heart Center approved the study proposal, and all the patients signed a written informed consent. The routine institutional perioperative monitoring was applied to all the participants, which included radial artery catheterization, five-lead electrocardiography, temperature monitoring, central venous pressure measurement, and pulse oximetry.

Anaesthesia

Anaesthesia was induced with midazolam 0.05 mg/Kg, fentanyl 5 µg/Kg, pancuronium 0.1 mg/Kg and thiopental 3-5 mg/Kg and was maintained with propofol infusion (5-10mg/Kg/h). Additionally, intermittent doses of fentanyl and pancuronium were prescribed at the discretion of an anesthesiologist. The intervention group received a bolus dose of 1mg/Kg of methylprednisolone over 10 minutes after the induction of anaesthesia, followed by a 2mg/Kg/d infusion for 24 hours. Control group received 15mg/Kg methylprednisolone as a single bolus dose after the induction of anaesthesia based on the current protocol of our center for all on-pump cardiac surgery patients, followed by an infusion of normal saline as placebo. The investigation team, which was different from the operating room anaesthesiologists, prepared and marked the syringes containing methylprednisolone or the placebo with letters A or B. The ICU physicians and other staff engaged in the care of the patients were kept blinded to the medication.

CABG and postoperative care

All the patients underwent median sternotomy and received routine CPB management. Use of the mammary artery or saphenous veins for grafting was left to the discretion of the surgeon. Both groups received of anticoagulants, inotropic and insulin during and after the operation under the protocol of Tehran Heart Center if needed. In the ICU, all the patients received routine care and extubation was performed based on our current protocol parameters. Management of blood glucose control, pain, mechanical ventilation, and discharge from the ICU was performed based on the protocols of our center.

Measurements

Hemodynamic indices, including heart rate, mean arterial blood pressure, and central venous pressures were recorded at baseline, during the operation and after the ICU admission. Blood samples for assessing serum creatinine levels were drawn before the induction of anaesthesia for baseline biochemistry measurements and were subsequently repeated at 24, 48 and 72 hours following CPB cessation. Arterial blood samples were drawn preoperatively to assess baseline arterial blood gas (ABG) indices in the room air. The PaO2 /FiO2 ratio and SpO2 were employed as oxygenation indices. These indices in conjunction with the ABG parameters were measured immediately after admission to the ICU, 6 hours later, while the patients were on the same ventilator setting at least for 10 minutes, and then 4 and 12 hours after extubation. In the case of any change in the

ventilation setting or decline of FiO2 in the extubated patients, the ABG measurement was repeated.

IL-6 and CRP were measured before the induction of anaesthesia as baseline and 6, 24, and 48 hours following CPB cessation. IL-6 concentrations were determined by the standard enzyme-linked immunosorbent assay (ELISA) (eBioscience, Austria). The kit's inter-assay and intra-assay coefficient of variation for the serum samples were 5.2% and 3.4%, respectively. Serum concentrations of CRP were determined by turbidimetry, and high sensitive CRP concentrations were measured by immuno-turbidimetry (Roche, Switzerland).

Statistical analysis

Statistical analysis was performed using SPSS software (Version15.0). The results are presented as mean ± standard deviation (SD) for the quantitative variables and frequency/percentages for the categorical variables. The data were analyzed using the independent samples t-test, chi-square or Fisher exact test, where appropriate, to evaluate inter-group differences. Additionally, the repeated measures ANOVA method was utilized for intra-group changes. A *P*-value <0.05 was considered statistically significant.

Results

A total of 72 patients were recruited in this study. Among them 35 patients were randomly assigned to the intervention and 37 to the control group. The characteristics of participants are presented in Table 1.

Table 1. Baseline characteristics and pre-operative measurements of the study population

Variable	Intervention (n=35)	Control (n=37)	*P*-value*
Baseline characteristics			
Male gender	28 (80.0%)	26 (70.3%)	0.34
Age, yr	57.57±9.55	63.68±8.59	0.006
Diabetes	15 (42.85)	14 (37.8)	0.42
Unstable angina	3 (8.57)	4 (10.81)	0.53
MI within 90 days	7 (20%)	12 (32.4 %)	0.23
Peripheral vascular disease	3 (8.57)	2 (5.40)	0.47
Pre-operative measurements			
Systolic BP, (mmHg)	132.78±20.38	125.23±23.06	0.16
Diastolic BP, (mmHg)	79.75±13.08	74.74±11.37	0.09
Mean arterial BP, (mmHg)	97.69±14.21	93.31±14.11	0.21
CVP, (cm H2O)	7.94±1.54	7.55±1.56	0.31
LVEF, (%)	47.33±7.90	50.10±8.35	0.16
Euroscore (additive)	2.77±2.26	3.56±2.04	0.12
pH	7.41±0.04	7.42±0.03	0.2
O2 Saturation, %	93.19±4.16	92.95±5.68	0.91
Blood sugar, (mg/dl)	120.47±38.26	112.69±26.03	0.61
Creatinine, (mg/dl)	0.88±0.27	0.95±0.25	0.29
CRP,(mg/l)	3.2±0.67	2.79±0.57	0.64
IL-6, (pg/l)	20.23±6.02	13.97±3.57	0.36
PaO2/FiO2	296.2±36.2	293.8±30.1	0.74

BP: Blood pressure; CRP: C-reactive protein; CVP: Central venous pressure; IL: Interleukin; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction.
*P <0.05 was considered as significant

Except for age, no difference was observed between the groups in sex, pre-existing medical conditions, preoperative medications, baseline ejection fraction, or surgical procedure. The intra-operative variables also

were similar between the groups, with no difference in the duration of anaesthesia or CPB, administration of crystalloids and blood products and intraoperative or ICU use of vasoactive medication. There was no difference between the two groups regarding the modes of ventilation, positive end-expiratory pressure (PEEP) and assisted spontaneous breathing (ASB) and Fio2. Furthermore, serum Cr levels had a similar trend in both groups. No significant difference was found about hyperglycemia and dose of insulin between the two groups. Comparison of the study variables in full detail is depicted in Table 2.

Table 2. Comparing the intra- and post-operative variables between the study groups

Variable	Intervention (n= 35)	Control(n= 37)	*P*-value*
Intraoperative			
Urine output (ml)	1029.69±574.71	1011.11± 502.01	0.88
CVP (cm H2o)	35.74±151.49	25.01±99.48	0.72
Arterial pressure (mmHg)	82.74±34.42	90.06±24.58	0.3
Aortic clamp time (min)	40.71±18.88	35.64±12.96	0.19
Pump Time (min)	68.66±33.13	66.30±18.17	0.63
Bleeding Volume (ml)	572.76±184.44	615.00±172.28	0.13
PaO2/FiO2 at anesthesia induction	3.11±0.62	3.39±0.74	0.09
Postoperative			
Bleeding (ml)	130.65±88.20	120.31±78.14	0.62
Blood product infusion (n, %)	7 (18.9%)	4 (11.4%)	0.51
Mechanical ventilation time(h)	9.66±3.92	10.83±4.33	0.23
Insulin prescription, n (%)	23 (65.7%)	28 (77.8%)	0.3
Insulin dose (u)	10.3 ± 7.02	7.89 ± 4.53	0.302
Heparin use, n (%)	7 (20 %)	15 (40.5%)	0.059
Diuretic use, n (%)	5 (14.3%)	7 (18.9 %)	0.59
Inotropic use, n (%)	31.40%	35.10%	0.8
Blood sugar (mg/dl)	175.39±26.03	175.60 ± 24.88	0.97
Serum Creatinine, 24h (mg/dl)	0.94±0.21	0.96±0.22	0.71
Serum Creatinine, 48h (mg/dl)	1.01±0.28	1.09±0.35	0.26
Serum Creatinine, 72h (mg/dl)	0.90±0.26	0.99±0.31	0.19
CRP, 6h (mg/l)	5.68±5.52	4.32±3.64	0.21
CRP, 24h (mg/l)	4.40±4.16	4.24±3.83	0.87
CRP, 48h (mg/l)	2.68±3.54	3.16±3.38	0.55
IL_6, 6h (pg/l)	84.16±49.03	92.27±63.89	0.54
IL_6, 24h (pg/l)	73.04±116.32	83.26±77.39	0.66
IL_6, 48h (pg/l)	54.33±54.11	37.94±31.23	0.11
CVP, (cm H2O)	9.54±3.13	9.82±3.30	0.71
ASB at ICU admission	10.2±0.90	10±0.00	0.20
ASB 6h after ICU admission	10.21±1.99	10.45±1.92	0.61
PEEP at ICU admission	4.94±0.33	5.15±0.85	0.19
PEEP 6h after ICU admission	5.18±0.76	5.00±0.00	0.17
PaO2/FiO2 at ICU admission	173.72±73.70	176.81±74.19	0.86
PaO2/FiO2 6h after ICU admission	274.20±95.84	269.95±75.12	0.83
PaO2/FiO2 4h after extubation	312.83±88.84	333.88±91.56	0.32
PaO2/FiO2 12h after extubation	37.49±11.39	35.65±9.58	0.47
Length of ICU stay (h)	29.85±12.44	26.39±8.65	0.19

ASB: assisted spontaneous breathing; CBP: Cardiopulmonary bypass; CRP: C-reactive protein; CVP: central venous pressure; IL: Interleukin; PEEP: positive end-expiratory pressure.
* P <0.05 was considered as significant

Baseline CRP concentrations were statistically similar in both groups, and the incline of CRP was not significantly different between the groups in the postoperative period, despite an increase in the first

post-CPB sampling (Figure 1-A). There was also no difference in the second and third post-CPB samples for CRP between the study groups (Table 2).

Baseline IL-6 concentrations were similar in both groups. As compared with the baseline values, a significant increase was found in the IL-6 levels within both groups (P<0.001 for both); however, the difference between the groups was not significant (P=0.54). Although not statistically significant, the 24-hour sample showed a larger decrease of IL-6 concentration in the intervention group compared to the control group. This decline continued into 48 hours after surgery (Figure 1-B) in both groups, which was not significant again.

Oxygenation indices (Pao2/Fio2) in the ICU, before and after extubation showed no significant difference. The length of ICU stay and other complications were similar for both groups, as is presented in Table 2. No case of postoperative infection or any other serious complication was reported.

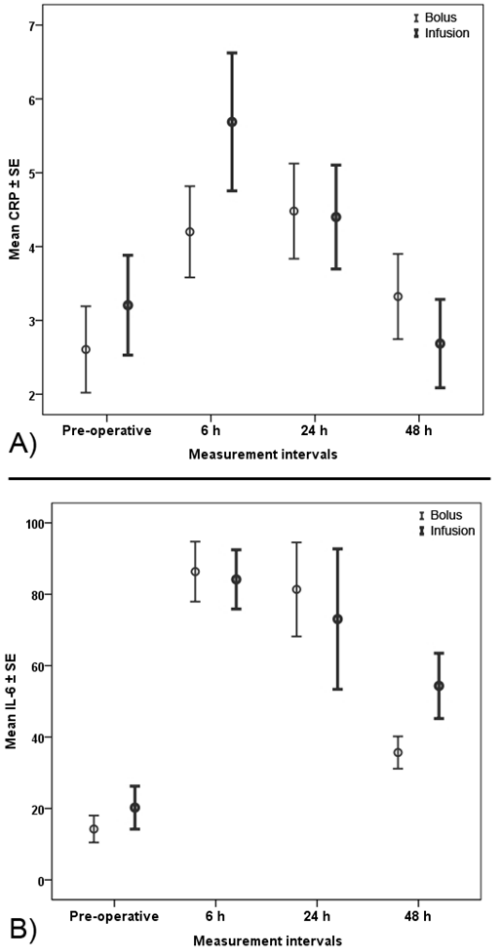

Figure 1. Comparison of the measurements of serum CRP (A) moreover, IL-6 (B) between the study groups

Discussion

In this study, authors investigated whether a continuous low-dose infusion of methylprednisolone is as effective as its high-dose bolus in attenuating the inflammatory response in CABG candidates. Current findings indicated that the levels of CRP and IL-6, as indices of inflammation, did not differ between the study groups. There was no difference between the two groups regarding early outcomes as evaluated by intubation time, oxygenation indices, length of stay in the ICU, and post-operative complications.

Although the use of corticosteroids during cardiac surgery is a controversial issue, they are commonly used in many centers to prevent cardiopulmonary adverse effects. There are some meta- analyses supporting the use of corticosteroids in cardiac surgery patients because of improvements in both morbidity and mortality (1). Despite different results of various studies (17), overall it seems that corticosteroids reduce perioperative morbidity (16,18).

In our hospital, anesthetists use corticosteroids for the prophylaxis in cardiac surgery patients undergoing CPB. We usually use high-dose methylprednisolone (15mg/kg as a single dose), and occasionally dexamethasone. Therefore, we could not assign a control group without receiving corticosteroids to compare the primary and second outcomes. However, some previous studies show that corticosteroids reduce perioperative morbidity (16, 18).

Various studies have been designed to determine the effect of corticosteroids on the postoperative inflammatory response, but they could not reach a consensus about the optimal steroid type, dose, and frequency of administration (1). It is known that a high dose of corticosteroids is associated with various side effects, such as a rise in the rate of infection and immunosuppression (11,19-22).Within the study period, we had no case of post-operative infection, including documented pneumonia or wound infection and nor was any significant difference between the two groups with respect to hyperglycemia and insulin dose. It is deserving of note, however, that our sample size might be too small.

The intubation time and length of ICU stay are commonly used in the ICU setting as the early outcomes. It has been shown that a low dose of corticosteroids is as effective as a high-dose in reducing the intubation time and arrhythmia in cardiac surgery patients, with lower potential side effects (11). Murphy *et al*., (23) evaluated the effect of low-dose

dexamethasone on quality of recovery in patients undergoing cardiac surgery and CPB and concluded that a low dose of dexamethasone significantly improve recovery quality on the first and second postoperative days. Moreover, there was no difference between the two groups in their study in terms of the length of stay in the ICU and hospital.

We could not find any significant difference between our two groups in the present study, regarding the early postoperative outcomes, including intubation time and the length of ICU stay.

Pulmonary dysfunction is one of the most important complications of CPB. The PaO2/FIO2 ratio is the main index of hypoxemia and marker of gas exchange in many studies as well as the present one. Some studies have claimed that the PaO2/FiO2 ratio depends both on the FiO2 level and on arterial oxygen saturation (24-27). Accordingly, we considered the SpO2, level of pressure support, and PEEP in case of any difference between the two groups. We could not detect any significant difference regarding pulmonary dysfunction as assessed by the PaO2/FIO2 ratio.

A low dose of methylprednisolone has been effective in reducing the inflammatory response. In a randomized trial conducted by Bourbon *et al*., (28), single doses of methylprednisolone (5 and 10 mg/kg) were compared with placebo in on-pump CABG patients. The inflammatory response was assessed by measuring TNF-α and IL-6. The authors found that the low dose of methylprednisolone (5 mg/kg) effectively reduced the increase in TNF-α and IL-6. In this study, the level of inflammatory mediators especially IL-6 remained elevated 24 hours after bypass.

In another clinical trial, a single low-dose injection of methylprednisolone was able to reduce the systemic inflammatory response and morbidity in on-pump cardiac surgery patients (29). None of these studies compared high-dose and low-dose corticosteroids, and this is one of the main strengths of the current study.

Continuous infusion of methylprednisolone in patients with early severe acute respiratory distress syndrome (ARDS) has been shown to be effective in the down-regulation of systemic inflammation and conferred a significant improvement in the pulmonary function and reduction in extra pulmonary organ dysfunction, duration of mechanical ventilation and, length of ICU stay (30). In that study, prednisolone was administered as an infusion in a loading dose of 1mg/kg, followed by an infusion of 1mg/kg/d for a week. Prednisolone was subsequently continued with a dose of 1-2 mg/kg/d for another week before it was tapered over 2 weeks. More recently, Seam *et al*., (31) evaluated the effect of a low-dose infusion of methylprednisolone on the markers of inflammation, coagulation, and angiogenesis during early ARDS in four ICUs. The dose of infusion was the same as that of the previous study. Low-dose methylprednisolone was associated with a lower mortality rate, mechanical ventilation duration, and lung injury score. Also, methylprednisolone decreased IL-6 levels. Generally the inflammation response to CPB is considered similar to ARDS. Based on the profile of the inflammatory biomarkers in a large number of studies, we hypothesized that a low-dose infusion of methylprednisolone over 24 hours might be more efficacious than high single doses in attenuating the inflammatory response after CPB, not least because it seems that the pharmacokinetic of drugs changes with CPB (32-33). It should be noted that the dose of methylprednisolone in the low-dose infusion group is around 1/20 of the high single dose.

In current study, IL-6 and CRP were selected as inflammatory biomarkers, because of their high correlation with inflammation in many studies. We found that both inflammatory markers profiles decreased in our patients following the administration of methylprednisolone that is consistent with other studies (34).

In the present study, we found significant elevations in IL-6 levels at six hours in both groups, but the elevated IL-6 levels, as well as serum CRP levels, did not significantly differ between two study groups. In conclusion, the infusion of a low-dose methylprednisolone had a similar effect in reducing the inflammatory response compared to the single high-bolus dose.

Study limitation

The major limitation of present study was the absence of a control group receiving placebo, for all our patients were given a loading dose of corticosteroids at the discretion of our anesthetists and in accordance with the current institutional policy. Nevertheless, according to the existing literature, it seems that corticosteroids can reduce inflammatory biomarkers and morbidity after CPB. Secondly, current sample size was small since we were able to enroll 72 patients as a result of administrative problems of providing the laboratory kits after the commencement of the trial. Another limitation was that we measured only two common biomarkers and, therefore, could not extrapolate current results to other markers of inflammation.

Based on present findings, a continuous low-dose infusion of methylprednisolone is as effective as a high-dose bolus in the attenuation of the inflammatory response. As much as our relatively small sample size precluded the detection of the regimen's advantages, such as lower rates of hyperglycemia and infection, at least the total dose of the drug in this method is much lower than the bolus dose. Furthermore, there was no difference between the two methods regarding the postoperative early outcomes. More studies with high and sufficient sample sizes are required to confirm these results. We recommend further larger studies to determine the effect of different corticosteroid administrating methods on pro- and anti-inflammatory cytokine levels and on the postoperative outcomes.

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