Effects of Corticosteroids on Inflammatory Response Following Cardiopulmonary Bypass

Darko Anić, Hrvoje Gašparović, Višnja Ivančan, Drago Batinić

Department of Cardiac Surgery and 1Department of Immunology, Clinical Institute of Laboratory Diagnosis, Zagreb University Hospital Center, Zagreb, Croatia

Aim. To investigate the effects of corticosteroids on the reduction of inflammatory response after cardiopulmonary bypass.

Methods. Twenty patients undergoing elective coronary revascularization were randomized into two groups, which both underwent coronary artery bypass surgery with the aid of normothermic cardiopulmonary bypass. One group received a single dose of methylprednisolone prior to normothermic cardiopulmonary bypass, whereas no steroid treatment was given to other group of patients. The two groups were comparable with respect to preoperative demographic data. Serum samples from all patients were drawn preoperatively and 3, 6, and 24 hours after the surgical procedure. The serum concentrations of tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), as well as the white blood cell count were measured. Serum C-reactive protein concentrations (CRP) were determined preoperatively and 72 hours postoperatively. Standard hemodynamic measurements for both groups were collected and analyzed.

Results. We did not find any increase in the postoperative concentrations of TNF-α and IL-1β in either group. The concentrations of IL-6 and IL-8 increased significantly in both groups, from immeasurable concentrations preoperatively to as high as 496 pg/mL for IL-6 and 128 pg/mL for IL-8 three hours after surgery. However, the observed increase was significantly smaller in the group of patients receiving methylprednisolone.

Conclusion. It seems that the administration of corticosteroids prior to the initiation of cardiopulmonary bypass may alleviate the intensity of the inflammatory response, as evidenced by reduced increase in inflammatory mediators.

Key words: cardiopulmonary bypass; cytokines; inflammation; interleukins; methylprednisolone; postoperative complications; tumor necrosis factor

Activation of complement, neutrophils, cytokines, kallikrein, and coagulation cascades, as well as free radical generation have been proposed to be responsible for the deleterious effects of cardiopulmonary bypass (1,2). The systemic response that follows cardiopulmonary bypass was associated with increased capillary permeability, leukocytosis, accumulation of interstitial fluid, and eventually organ impairment (1). The fully developed clinical picture, often called post-perfusion syndrome, is characterized by pulmonary dysfunction, renal insufficiency, and a bleeding diathesis (3). This study focuses on the role of cytokines as mediators of the systemic inflammatory response after cardiopulmonary bypass. Cytokines are endogenous polypeptides produced by a wide variety of cells and especially by activated monocytes and macrophages. Interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) are cytokines involved in the induction of the inflammatory response in patients undergoing cardiac surgery (4,5). Interleukin-1β (IL-1β) is involved in the activation of cell-mediated immune response and release of acute-phase proteins. In addition, IL-1β enhances the production of other cytokines. IL-6 is a pleiotropic cytokine engaged in the differentiation of B lymphocytes, T-cell proliferation, and synthesis of acute phase proteins. IL-8 is an important activator of neutrophils, with a chemotactic effect. TNF-α acts synergistically with IL-1β in the activation and regulation of the host response (6), and is associated with the initiation of disseminated intravascular coagulation in septic shock.

Corticosteroid treatment is thought to decrease the intensity of the systemic inflammatory response by several mechanisms, including inhibition of the complement and arachidonic acid systems and suppression of the transcription of activation genes for multiple inflammatory cytokines (3,4,7,8).

The aim of our study was to assess suppressive effects of methylprednisolone administered prior to
normothermic cardiopulmonary bypass on the release of systemic inflammatory response mediators IL-1β, IL-6, IL-8, and TNF-α by determining the serum concentrations of these cytokines before and after cardiac surgery.

**Patients and Methods**

**Patients**

Twenty patients selected for elective isolated coronary revascularization at the Department of Cardiac Surgery, Zagreb University Hospital Center, were included into the prospective study between March 1 and May 1, 1996 (Table 1). We used a list of computer-randomized odd and even numbers to allocate study between March 1 and May 1, 1996 (Table 1). We used a list of computer-randomized odd and even numbers to allocate patients into two equally sized groups. The investigation was approved by the Zagreb University Hospital Center Ethics Committee. Patients receiving corticosteroid treatment and those suffering from diabetes mellitus were excluded from the study. All patients prior to inclusion were carefully evaluated for signs of infection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Methylprednisolone treatment</th>
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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.0±8.9</td>
<td>57.0±10.0</td>
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<tr>
<td>Men/women (n)</td>
<td>8/2</td>
<td>6/4</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>48.0±12.3</td>
<td>52.5±9.2</td>
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<td>Cross clamp time (min)</td>
<td>31.7±9.6</td>
<td>30.0±11.3</td>
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<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>57.4±12.0</td>
<td>59.9±16.2</td>
<td></td>
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<tr>
<td>No. of grafts</td>
<td>3.2±0.6</td>
<td>3.0±0.9</td>
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</table>

**Anesthetic Technique**

Anesthetic regimens did not differ between the two groups. Induction was achieved with midazolam (0.1 mg/kg), fentanyl (10-15 μg/kg), and pancuronium (0.15 mg/kg). Anesthesia was maintained with inhalation agents, as well as repeated doses of fentanyl and pancuronium. Initial anticoagulation included 3 mg/kg of heparin to achieve an activated clotting time of 450 s or greater. A Swan-Ganz catheter was introduced into the pulmonary artery with the aim of monitoring hemodynamic performance.

**Cardiopulmonary Bypass**

A standard cardiopulmonary bypass circuit was used, consisting of a roller pump Sarns 9000 Perfusion System, Ann Arbor, MI, USA; polyvinyl chloride (PVC) tubing (Dideco, Mirandola, Italy); and membrane oxygenator (Dideco). A non-pulsatile flow of 2.4 L/min/m² was maintained. Patients in both groups underwent conventional coronary artery bypass surgery with the aid of normothermic cardiopulmonary bypass. Warm blood cardioplegia was used for myocardial protection in all patients. Distal anastomoses were completed during a single period of aortic cross clamping. A partial-occlusion aortic clamp was used for the creation of proximal anastomoses during reperfusion.

Patients in one group received a single dose of methylprednisolone (30 mg/kg) prior to induction of anesthesia, whereas the patients in the other group did not receive any corticosteroid either before or after the surgical procedure.

**Cytokine Analysis**

Blood samples were drawn either from the radial artery line or the arterial line of the extracorporeal circuit. Samples were drawn preoperatively and 3, 6, and 24 hours following the coronary revascularization procedure. The concentrations of cytokines were quantified by enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Qantikine, Minneapolis, MN, USA). The detection range was 3.9-250.0 pg/mL for IL-1β; 3.1-300.0 pg/mL for IL-6; 3.1-20,000.0 pg/mL for IL-8; and 15.6-1,000.0 pg/mL for TNF-α. In addition, serum concentrations of C-reactive protein were determined preoperatively and 72 h after surgery by using Olympus immunochemistry system (Olympus AU 400, Olympus Diagnostica GmbH, Hamburg, Germany).

**Postoperative Management**

After the operation, the patients were transferred to the cardiac intensive care unit. Standard hemodynamic monitoring included recording of the cardiac index, systemic vascular resistance, and pulmonary and systemic blood pressures. Inotropic medication was instituted if required. Intravenous nitroglycerin was used for the control of hypertension. All patients were transferred to the step-down unit as soon as feasible.

**Statistical Analysis**

Demographic data were expressed as mean±standard deviation. Intra-operative data were presented graphically (median, range). Kruskal-Wallis and Mann-Whitney tests were used for the comparison between the groups. Further statistical analysis included the Wilcoxon and chi-square tests. P-value <0.01 was considered statistically significant. MedCalc statistical package (MedCalc Inc., Mariakerke, Belgium) was used for all statistical analyses.

**Results**

The concentrations of IL-1β and TNF-α remained below the lowest measurable value in all patients, ie, below 3.9 pg/mL and 15.6 pg/mL respectively. The preoperative concentrations of IL-6 were low and measurable in only four patients. Following the procedure, the concentration of IL-6 increased sharply and peaked three hours postoperatively. A statistically significant difference between the two groups was observed in the concentrations of IL-6 at three and six hours postoperatively (Fig. 1).

![Figure 1. Serum concentrations of interleukin-6 (median, range) in relation to cardiopulmonary bypass and steroid administration in 10 patients who received (closed triangles) and 10 patients who did not receive (open squares) methylprednisolone preoperatively. Asterisk indicates p<0.01, Wilcoxon test.](image)

A similar pattern was seen in the post cardiopulmonary bypass concentrations of IL-8 (Fig. 2). The highest concentration was demonstrated three hours after surgery in both groups. IL-8 levels were detectable in only three patients preoperatively.

There was an initial increase in the leukocyte count after the surgical procedure in both groups. The most pronounced difference between the groups was observed 24 h postoperatively, when the white blood cell count was significantly higher in the group that received methylprednisolone (Fig. 3). The median concentration of C-reactive protein measured preoperatively in the group receiving steroids was 2 mg/L (range, 1-49), and 3 mg/L (range, 1-12) in the group.
that did not receive steroids preoperatively. C-reactive protein was also measured 72 h after conventional coronary revascularization, when its median value in the steroid-receiving group was 33 mg/L (range, 13-79) and 120 mg/L (range, 28-284) in the non-steroid group. Although it increased in both groups, the increase was significantly smaller in the group that received steroids preoperatively (Wilcoxon test, \( p<0.01 \)).

There was no correlation between peak concentrations of IL-6 or IL-8 and cardiopulmonary bypass or aortic clamping durations. No correlation was found between IL-6 and IL-8 concentrations and mean arterial pressure, cardiac output, or systemic vascular resistances (data not shown).

**Discussion**

The exposure of blood to artificial surfaces, as in extracorporeal circuits, activates complement, kallikrein systems, and coagulation and fibrinolytic cascades (9-11). Normothermic cardiopulmonary bypass for conventional coronary revascularization is a well-established alternative to hypothermic cardiopulmonary bypass. Frering et al (12) found that the production of circulating inflammatory cytokines in response to cardiopulmonary bypass is independent of the body temperature. In contrast to this data, Chello et al (13) showed that the activation of the complement system was more pronounced in patients undergoing normothermic cardiopulmonary bypass than in the control hypothermic group.

There are controversial data in the literature on IL-1β and TNF-α as mediators of the post-cardiopulmonary bypass inflammatory syndrome. In several studies, the concentrations of these cytokines were undetectable (6,14-17); other studies demonstrated an increase in their serum concentrations (18,19). In our investigation, the serum concentrations of IL-1β and TNF-α remained below the detectable levels. It seems that a significant increase in the circulation concentrations of these cytokines accompanies severe cases of the systemic inflammatory response syndrome (20,21). All patients in our study had an uneventful postoperative course, which might explain why the levels of IL-1β and TNF-α remained undetectable.

The serum concentration of IL-6 increased sharply and peaked three hours after the surgical procedure. This increase was abated by preoperative methylprednisolone administration. A decrease in the concentrations of IL-6 was noted at six hours postoperatively. As this declining pattern continued, the concentrations measured 24 hours postoperatively approached preoperative values.

The activation of neutrophils following cardiopulmonary bypass leads to the release of lactoferrin, elastase, and myeloperoxidase (15,22,23). Because IL-8 plays a major role in the activation of neutrophils, its concentrations may be reflective of the severity of the inflammatory response. In our study, the concentrations of IL-8 were measurable preoperatively in only three patients. The time course of IL-8 changes after cardiopulmonary bypass was similar to that of IL-6. An abrupt increase in the concentration was observed three hours after surgery, but declined thereafter. Similar findings were observed in other studies (17,24,25). Although the increase in the IL-8 concentration was suppressed in the group of patients receiving steroids, the difference was not statistically significant. C-reactive protein is a major acute-phase protein whose synthesis is induced by proinflammatory cytokines IL-1, IL-6, and TNF-α. It has been associated with opsonization and activation of the classical complement pathways by binding C1q to augment opsonization (26,27). The concentration of C-reactive protein after surgery has been reported to peak much later than cytokines (15). In our study, the concentration of C-reactive protein was measured 72 h after the procedure, when it increased in both groups. The concentration of C-reactive protein was, however, significantly lower in the steroid group due to decreased concentration of IL-6 (28).

Although the practice of administering corticosteroids prior to open heart surgery has not been universally accepted, it is advocated in many "fast-track"
protocols (29). Based on our results, we believe that if a cross-clamp or a cardiopulmonary bypass time is relatively short the systemic inflammatory response can not provoke substantial damage. That is why the influence of corticosteroids reflects only on some cytokine levels and not on clinical findings.

References

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Correspondence to:
Darko Anić
Department of Cardiac Surgery
Zagreb University School of Medicine
Kušpićeva 12
10000 Zagreb, Croatia
danic@hi.hinet.hr