Combined Steroid Treatment for Congenital Heart Surgery Improves Oxygen Delivery and Reduces Postbypass Inflammatory Mediator Expression

Valerie A. Schroeder, MD, MS; Jeffery M. Pearl, MD; Steven M. Schwartz, MD; Thomas P. Shanley, MD; Peter B. Manning, MD; David P. Nelson, MD, PhD

Background—Steroid administration during cardiopulmonary bypass is thought to improve cardiopulmonary function by modulating bypass-related inflammation. This study was designed to compare preoperative and intraoperative methylprednisolone (MP) to intraoperative MP alone with respect to postbypass inflammation and clinical outcome.

Methods and Results—Twenty-nine pediatric patients undergoing bypass procedures were randomly assigned to receive preoperative and intraoperative MP (30 mg/kg 4 hours before bypass and in bypass prime, n=14) or intraoperative MP only (30 mg/kg, n=15). Myocardial inflammatory mediator mRNA expression was determined in paired atrial biopsies (before and after bypass) by ribonuclease protection. Before and after bypass, serum IL-6 and IL-10 were measured by ELISA. Postoperative outcome was assessed by intubation time, CICU length of stay, fluid balance, arterio-venous $O_2$ difference ($\Delta A-\dot{V}O_2$), and inotrope requirements. Compared with intraoperative MP alone, combined preoperative and intraoperative MP was associated with reduced myocardial mRNA expression for IL-6, MCP-1, and ICAM-1 both before and after bypass ($P<0.05$). Patients who received combined steroids had lower serum IL-6 and increased IL-10 at end-bypass ($P<0.05$), although differences were negligible by 24 hours. Combined MP treatment was associated with reduced fluid requirements, lower body temperature, and lower $\Delta A-\dot{V}O_2$ for the first 24 hours after surgery ($P<0.05$), along with trends toward improvement in other clinical outcomes.

Conclusions—Compared with intraoperative steroid treatment, combined preoperative and intraoperative steroid administration attenuates inflammatory mediator expression more effectively and is associated with improved indexes of $O_2$ delivery in the first 24 hours after congenital heart surgery. These findings need to be confirmed in a larger multicenter trial. (Circulation. 2003;107:2823-2828.)

Key Words: cardiopulmonary bypass ■ heart defects, congenital ■ interleukins ■ inflammation

Repair or palliation of congenital heart disease often requires cardiopulmonary bypass and myocardial ischemia. Transient postoperative contractile dysfunction is common, and $\approx25\%$ of pediatric patients have low cardiac output syndrome (LCOS). Myocardial dysfunction and tissue injury after heart surgery arises primarily from bypass-related inflammation. The degree of injury is thought to depend on the extent of the inflammatory response, which has prompted various antiinflammatory strategies such as heparin-coated bypass circuits, ultrafiltration, aprotinin, leukocyte-endothelial–blocking agents, and intraoperative steroids. Although steroids have been used for years to attenuate postbypass inflammation, data to support this stem almost entirely from trials in adults with coronary artery disease. Even in adults, steroid use for cardiac surgery is controversial, and data in children are minimal. In adults, perioperative steroid administration reduces circulating proinflammatory cytokines (eg, TNF-$\alpha$, C5a, IL-6, IL-8), increases serum antiinflammatory cytokines (eg, IL-10, IL-4), and improves myocardial perfusion and function, but data on intubation time and ICU length of stay are discordant. The only study of steroid treatment for congenital heart surgery found that children receiving a single dose of dexamethasone 1 hour before bypass had reduced fluid requirements, lower body temperature, shorter intubation time, and lower troponin, IL-6, and TNF-$\alpha$ levels.

Previous clinical studies have chiefly compared placebo with steroid administration during or immediately preceding bypass. Recent data from animal models suggest that combined preoperative and intraoperative steroid administration may provide superior antiinflammatory benefits. Studies in adult cardiac surgery patients comparing multidose preoperative and intraoperative steroid treatment to placebo are limited, and there are no published data in adults or...
children comparing multidose preoperative/intraoperative steroid therapy to a single-dose of steroids administered before or during bypass. The rationale for combined preoperative and intraoperative steroid therapy is that this may inhibit activation of bypass-mediated inflammatory cascades more effectively than intraoperative treatment alone. To test whether combined preoperative and intraoperative methyl-prednisolone is superior to intraoperative methylprednisolone alone, a prospective, randomized trial was performed to compare inflammatory mediator induction and clinical outcome. To assess the myocardial inflammatory response, transcript expression of selected inflammatory mediators was assessed in paired atrial samples obtained before and after bypass. Since the peak effect of methylprednisolone occurs 1 to 4 hours after administration and the duration of action is 12 to 24 hours, preoperative methylprednisolone was administered 4 hours before bypass initiation. The key finding was that children treated with combined preoperative and intraoperative methylprednisolone had reduced myocardial inflammatory mediator expression and improved indices of O2 delivery in the early postoperative period when low cardiac output syndrome is common.

Methods

Study Design

The study was approved by the Children’s Hospital Institutional Review Board, and informed consent was obtained. Twenty-nine children undergoing cardiopulmonary bypass (CPB) for repair of congenital heart disease were enrolled. Patients were stratified for cardiac diagnosis and randomly assigned in a double-blind manner to receive preoperative and intraoperative methylprednisolone (MP, 30 mg/kg 4 hours before bypass and in bypass prime, n = 14) or intraoperative MP only (placebo 4 hours before bypass and 30 mg/kg MP in bypass prime, n = 15). Exclusion criteria included sepsis, chronic or acute lung disease, gastrointestinal bleeding, immunodeficiency, steroid use, or cardiac arrest within 1 week before surgery.

Intraoperative Management

Balanced general anesthesia was attained with fentanyl, muscle relaxant, and isoflurane. Aprotinin was administered to infants <2 months old. Full-flow bypass with moderate hypothermia was used for circulatory support. Cold-blood cardioplegia with additional dosing at 20- to 30-minute intervals was given during aortic cross-clamping. Cardioplegia was delivered antegrade except in arterial switch operations, in which retrograde cardioplegia was used after initial dose. Ultrafiltration (UF) was used in all cases; both conventional and modified UF (after bypass termination) was used in all cases except arterial switch operations, in which conventional UF alone was used during rewarming.

Postoperative Management

Patients were ventilated with 20 mL/kg tidal volume and ventilator rate was adjusted to control pCO2. Inotropic support and volume were managed by the attending physician. Diuretic therapy was initiated routinely on postoperative day 1.

Data Collection

Body temperature, inotrope dosage, and fluid input/output were collected from nursing records. Laboratory analyses were performed in the central laboratory. Creatinine clearance (CrCl) was calculated as CrCl = k × L × PCr (where k is a constant 0.45 for infants and 0.55 for children, L is height in centimeters, and PCr is plasma creatinine). To quantify inotropic support, inotrope scores were calculated as the sum of all inotrope doses, correcting for potency (dopamine, dobutamine, amrinone=1, milrinone=15, epinephrine=100). Inotrope data were also used to assess whether patients had LCOS during the first 24 hours after surgery. With the use of the criteria developed for the PRIMACORP study, LCOS was determined as the clinical signs of low output (eg, tachycardia, oliguria, poor perfusion, metabolic acidosis or widened ΔA–V02), which necessitates significant change in medical support by the blinded attending physician, including increased doses of an initial inotropic agent (>100% above baseline) or administration of an additional inotropic agent.

As an index of systemic O2 delivery, arterial-venous O2 content difference (ΔA–V02) and O2 extraction ratio (OER) were calculated for the first 24 hours after surgery. Co-oximetry was used to measure arterial and SVC saturation and hemoglobin (SaO2, SsvcO2, Hgb). ΔA–V02 and OER were determined as CaO2–CsvcO2 and (CaO2–CsvcO2)/CaO2, where CaO2=arterial O2 content (1.36 × Hgb × SaO2) and CsvcO2 = mixed-venous O2 content (1.36 × Hgb × SsvcO2). Superior vena cava (SVC) samples were used as the mixed-venous sample since SVC and PA saturation are known to correlate closely in pediatric patients.

Figure 1. Myocardial inflammatory mediator expression in patients treated with intraoperative MP or combined preoperative and intraoperative MP (mean ± SD). Total RNA isolated from paired atrial samples obtained before and after bypass was assessed by RNase protection. Although both groups had post-bypass induction of inflammatory mediators, patients receiving combined MP had lower expression of all inflammatory mediators at end-bypass, with RANTES, MCP-1, IL-6, and ICAM-1 reaching statistical significance (P < 0.05). Furthermore, antiinflammatory efficacy of preoperative steroid treatment was detectable even before bypass; patients receiving combined MP had lower MCP-1, IL-6, and ICAM-1 expression at initiation of bypass (before any myocardial ischemia).
RNase Protection Assay
Paired atrial samples were collected at initiation and end-CPB and preserved in RNA Later solution (Ambion). Total RNA was isolated, and 15 μg of each sample was analyzed by Multiplex RNase protection (Pharmingen).21 Signal intensities detected by Phosphorlmager were analyzed by Imagequant software (Molecular Dynamics). GAPDH expression was used to control for loading.

Enzyme-Linked Immunosorbent Assay
Serum IL-6 and IL-10 levels were determined at the following time points: preoperative (before study drug infusion), end-CPB, and 4 and 24 hours after CPB. Duplicate analyses were performed with commercially available ELISA kits (R&D Systems).

Statistical Analysis
Differences between groups were determined by Student’s t test, χ2 (for categoric variables), or Mann-Whitney rank-sum test (nonnormal distribution). For data with repeated measurement over time, repeated-measures ANOVA was used for overall group differences. A probability value of <0.05 was considered statistically significant.

Results
Twenty-nine pediatric patients were randomly assigned to receive intraoperative MP (n=15) or combined preoperative and intraoperative MP (n=14). Patient age, gender, support times, and cardiac diagnoses were evenly distributed between the two groups (Tables 1 and 2), although the combined dose group tended to be younger (P=0.069).

Patients receiving combined preoperative and intraoperative steroid therapy had lower myocardial inflammatory mediator mRNA expression before and after bypass (Figure 1). RNase protection assessed inflammatory mediator expression in paired atrial samples obtained before and after bypass. Although myocardial inflammatory mediator expression was induced by bypass in both treatment groups, end-bypass expression of all inflammatory mediators tended to be lower in the combined steroid group, with RANTES, MCP-1, IL-6, and ICAM-1 reaching statistical significance. Furthermore, preoperative steroid treatment had antiinflammatory effects even before bypass; patients receiving preoperative steroids had lower mRNA expression for MCP-1, IL-6, and ICAM-1 at bypass initiation (before myocardial ischemia).

Serum IL-6 and IL-10 were also altered in patients who received combined steroids (Figure 2). Baseline IL-6 and IL-10 was similar for both groups. Serum IL-6 was lower at end-CPB and 4 hours after CPB in patients who received combined steroids, but IL-6 was equally elevated in both groups by 24 hours. Compared with intraoperative therapy alone, patients receiving combination therapy had a greater increase in the antiinflammatory cytokine IL-10 at end-CPB, but levels returned to baseline by 24 hours after CPB in both groups.

Alteration in myocardial and systemic inflammatory mediators with combined steroid therapy was associated with improvement in certain clinical parameters. Compared with intraoperative therapy alone, patients who received combined steroid therapy had lower ΔA VO2 and lower O2 extraction ratio during the first 24 hours after surgery (Figure 3, P<0.05, repeated-measures ANOVA). Enhanced ΔA VO2 and O2 extraction was observed even though the combined steroid group required less fluid (P=0.027). Patients receiving combined steroid therapy also tended to have a shorter CICU length of stay (6.1 versus 4.4 days, P=0.07) and a lower incidence of LCOS (40% versus 14%, P=0.11), although these failed to reach statistical significance. Average and maximal body temperature of patients who received combined steroids were significantly lower than patients who received intraoperative steroids only (P=0.007 and 0.043), and patients who received combined steroids were less likely

TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Intraoperative Methylprednisolone Only (n=15)</th>
<th>Combined Preoperative/Intraoperative Methylprednisolone (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>4.4±3.9</td>
<td>2.1±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male:female</td>
<td>11:5</td>
<td>7:7</td>
<td>NS</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>169±53</td>
<td>168±53</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>109±29</td>
<td>109±40</td>
<td>NS</td>
</tr>
<tr>
<td>Aprotinin (% of patients receiving)</td>
<td>33% (5/15)</td>
<td>50% (7/14)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

TABLE 2. Diagnoses and Operative Procedures

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>Intraoperative Methylprednisolone Only</th>
<th>Combined Preoperative/Intraoperative Methylprednisolone</th>
<th>Operative Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transposition of the great arteries</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>Arterial switch</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>Complete tetralogy of Fallot repair</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Rastelli</td>
</tr>
<tr>
<td>Atrioventricular canal defect</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>Atrial and ventricular septal defect closure</td>
</tr>
<tr>
<td>Total patients</td>
<td>15</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prolonged length of stay tended to be shorter in patients who received combination therapy (6.1 days versus 7.4 days, P=0.07).
to have a temperature spike >38°C during the first 24 hours after surgery than patients who received intraoperative steroids only (2/14 versus 10/15 patients, P = 0.004). There were no differences between the two groups for intubation time, inotrope use, creatinine clearance, serum lactate, or serum Troponin I (Figure 3 and Table 3).

All patients survived to discharge. Two patients (one from each treatment group) had transient postoperative seizure activity. The sole documented infection in the study occurred in a patient receiving intraoperative therapy only and was successfully treated with antibiotics. There was no incidence of hypertension, gastrointestinal bleeding, surgical wound breakdown, glucosemia, or electrolyte imbalances as a result of study medications.

**Discussion**

In this randomized study of pediatric cardiac surgery patients, the efficacy of combined preoperative and intraoperative steroid therapy was compared with intraoperative steroid treatment alone. Since the peak effect of intravenous methylprednisolone occurs ~1 to 4 hours after administration,19,20 the working hypothesis was that combined steroid therapy inhibits activation of bypass-mediated inflammatory cascades more effectively than intraoperative therapy alone. Patients treated with combined preoperative and intraoperative methylprednisolone had lower myocardial and systemic inflammatory mediator expression, which corresponded to enhanced indices of O₂ delivery, lower body temperature, reduced fluid requirements, and a trend toward shorter CICU length of stay.

Pediatric patients receiving preoperative and intraoperative methylprednisolone had reduced serum IL-6 and increased antiinflammatory serum IL-10. These cytokine alterations were anticipated, since perioperative steroids in adults are known to alter circulating cytokine levels.4,8,12,16 The novel observation, however, is that combined steroid treatment reduces inflammatory mediator expression in the heart directly. Furthermore, steroid pretreatment reduces myocardial inflammatory mediator expression before bypass, thus indicating that antiinflammatory effects of preoperative steroid treatment precedes both myocardial ischemia and activation of blood elements by the extracorporeal circuit. Evidence of myocardial inflammation before cardiac surgery has been reported in children with heart defects.24,25 Accordingly, preoperative steroid treatment may attenuate ongoing systemic or local inflammation present before surgery. Preoperative steroids may also optimize antiinflammatory activity before further obligate inflammatory stimuli. Although steroids blunt adhesion molecule induction in vascular smooth...
In summary, compared with intraoperative methylprednisolone alone, combined preoperative and intraoperative

TABLE 3. Clinical Outcome Data

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Intraoperative MP Only</th>
<th>Combined Preoperative and Intraoperative MP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CICU length of stay, d</td>
<td>6.1±2.8</td>
<td>4.4±1.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Mechanical ventilation, h</td>
<td>85±71</td>
<td>74±52</td>
<td>0.66</td>
</tr>
<tr>
<td>Incidence of LCOs, % of patients</td>
<td>40% (6/15)</td>
<td>14% (2/14)</td>
<td>0.11</td>
</tr>
<tr>
<td>Inotrope score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h after CPB</td>
<td>15.3±6.8</td>
<td>13.1±5.7</td>
<td>0.37</td>
</tr>
<tr>
<td>48 h after CPB</td>
<td>15.3±8.3</td>
<td>13.5±5.1</td>
<td>0.49</td>
</tr>
<tr>
<td>Serum troponin I, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-CPB</td>
<td>285±380</td>
<td>210±224</td>
<td>0.53</td>
</tr>
<tr>
<td>4 h after CPB</td>
<td>147±106</td>
<td>127±95</td>
<td>0.61</td>
</tr>
<tr>
<td>24 h after CPB</td>
<td>64±35</td>
<td>62±42</td>
<td>0.92</td>
</tr>
<tr>
<td>Body temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVG first 24 h after CPB, °C</td>
<td>37.1±0.3</td>
<td>36.4±0.3</td>
<td>0.007</td>
</tr>
<tr>
<td>TMAX first 24 h after CPB, °C</td>
<td>38.1±0.5</td>
<td>37.4±0.7</td>
<td>0.043</td>
</tr>
<tr>
<td>Fluid input/output over first 24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid input, mL/kg per d</td>
<td>134±25</td>
<td>111±30</td>
<td>0.027</td>
</tr>
<tr>
<td>Fluid output, mL/kg per d</td>
<td>67±15</td>
<td>76±26</td>
<td>0.31</td>
</tr>
<tr>
<td>Total fluid balance, mL/kg per d</td>
<td>67±33</td>
<td>35±42</td>
<td>0.029</td>
</tr>
<tr>
<td>Estimated creatinine clearance, mL/min per m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCU admit</td>
<td>73±24</td>
<td>68±23</td>
<td>0.59</td>
</tr>
<tr>
<td>24 h after CPB</td>
<td>58±29</td>
<td>56±25</td>
<td>0.81</td>
</tr>
<tr>
<td>48 h after CPB</td>
<td>59±26</td>
<td>55±22</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. CICU indicates cardiac intensive care unit; TAVG, average body temperature over first 24 hours after CPB; TMAX, maximum body temperature over first 24 hours after CPB.

muscle and endothelium in vitro,26,27 effects on human myocardium have not previously been reported. In sum, the data support the hypothesis that combined preoperative and intraoperative steroid administration reduces bypass-related inflammation more effectively than intraoperative treatment alone.

Attenuation of myocardial inflammatory mediator expression with combined steroid therapy was associated with improved indices of O₂ delivery, reduced fluid requirements, and a trend toward shorter CICU length of stay, suggesting that modulation of bypass-mediated inflammation is clinically beneficial in pediatric patients. Compared with intraoperative steroid treatment alone, combined dose therapy was associated with lower ΔA VO₂ and systemic O₂ extraction in the early postoperative course, indicating lower systemic O₂ consumption and/or better systemic O₂ delivery. Although not measured in this trial, combined steroid treatment may attenuate hyperthermia-related increases in systemic O₂ consumption by reducing inflammation-related pyrexia.28 Furthermore, the data suggest that combined steroid treatment preserves myocardial performance by modulating bypass-mediated inflammation. In neonatal swine subjected to bypass and circulatory arrest, steroid administration attenuates myocardial inflammatory mediator expression, cardiomyocyte apoptosis, and myocardial troponin degradation.20,30 Steroids could also enhance myocardial performance through other mechanisms such as neuroendocrine effects or adrenergic receptor induction. Even without cardiopulmonary bypass, stress-dose steroids can lower inotrope requirements in pediatric cardiac patients with marginal cardiac output.22

Regardless of mechanism, the data highlight potential benefits of combination steroid treatment in pediatric cardiac surgery patients.

Since intraoperative steroid treatment is routine at our institution, an important limitation of this study is the absence of a control group of patients not receiving steroids. Although the data suggest that steroid treatment modulates postbypass inflammation, one cannot definitively conclude that steroid treatment is superior to placebo, nor does the study rule out the possibility that a single preoperative dose is as effective as intraoperative or multidose steroid treatment. The small sample size is another significant limitation of the study. Since the study population consisted of a complex mixture of patients, factors such as cardiac diagnosis, perfusion strategy, ultrafiltration, preoperative morbidity, or residual postoperative lesions could confound observations in such a small trial. We would emphasize that the findings should be confirmed in a larger multicenter trial. Another limitation is that myocardial inflammatory mediator expression was inferred from atrial tissue alone. Although only atrial myocardium was assayed, prior data suggest similar expression of markers such as IL-6, ICAM-1, and E-selectin in atrial and ventricular myocardium.31 Finally, mRNA transcriptional changes may not reflect changes in protein translation. The limited size of the tissue samples did not allow parallel protein expression analyses.

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methylprednisolone administration was associated with reduced myocardial and systemic inflammatory mediator expression. Steroid treatment also promotes synthesis of the anti-inflammatory cytokine IL-10. Attenuation of inflammatory mediator expression was associated with improved indices of O₂ delivery, reduced fluid requirements, lower body temperature, and trends for improvement in other clinical outcomes. Compared with intraoperative steroid administration, combined preoperative and intraoperative steroid treatment attenuates systemic and myocardial inflammatory mediator expression more effectively and is associated with improved indices of O₂ delivery in the first 24 hours after congenital heart surgery. These findings need to be confirmed in a larger multicenter trial.

Acknowledgments
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References
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