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Administration of Steroids in Pediatric Cardiac Surgery: Impact on Clinical Outcome and Systemic Inflammatory Response

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Abstract. Cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response. Pre-bypass steroid administration may modulate the inflammatory response, resulting in improved postoperative recovery. We performed a prospective study in the departments of cardiovascular surgery and pediatric intensive care medicine of two university hospitals that included 50 infants who underwent heart surgery. Patients received either prednisolone (30 mg/kg) added to the priming solution of the cardiopulmonary bypass circuit (steroid group) or no steroids (nonsteroid group). Clinical outcome parameters include therapy with inotropic drugs, oxygenation, blood lactate, glucose, and creatinine, and laboratory parameters of inflammation include leukocytes, C-reactive protein, and interleukin-8. Postoperative recovery (e.g., the number, dosage, and duration of inotropic drugs as well as oxygenation) was similar in patients treated with or without steroids when corrected for the type of cardiac surgery performed. After CPB, there was an inflammatory reaction, especially in patients with a long CPB time. Postoperative plasma levels of interleukin-8 were correlated with the duration of CPB time ($r = 0.62$, $p < 0.001$). Administration of steroids had no significant impact on the laboratory parameters of inflammation. Administration of prednisolone into the priming solution of the CPB circuit had no measurable influence on postoperative recovery and did not suppress the inflammatory response.

Key words: Congenital heart disease — Cardiopulmonary bypass — Inflammation — Glucocorticoids

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Cardiac surgery with the aid of cardiopulmonary bypass (CPB) leads to an acute inflammatory response associated with activation of complement, release of cytokines and chemokines into the circulation, as well as activation of inflammatory cells [14, 21]. Elevated levels of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-6, and IL-8, have been reported [6, 11]. This inflammatory response is counterbalanced by a complex system of inhibitors, such as IL-10 and soluble cytokine receptors [7, 10, 25].

Several therapeutic aspects have been proposed to modulate the inflammatory response, such as hemofiltration [12] or the use of various pharmacological agents, including steroids [17], nonsteroidal anti-inflammatory drugs [28], pentoxyphylline [5], aprotinin [22], or complement receptor blocking agents [2]. Although steroids have been used for years to attenuate post-bypass inflammation, data to support this derive 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 rare.

The aim of this prospective study was to analyze clinical parameters of outcome as well as markers of inflammation with and without pre-bypass administration of steroids in infants undergoing heart surgery with CPB.

Patients and Methods

Patients and Blood Sampling Protocol

The study was carried out at two cardiovascular surgery units and pediatric intensive care units. The study was approved by the local

Table 1. Patient characteristics

	Steroid group (n = 24)	Nonsteroid group (n = 26)	p value
Age (months)	5.0 (4.0–7.3)	21.5 (8.3–48.8)	0.0015
Body weight (kg)	5.8 (4.6–6.4)	11.4 (7.5–15.5)	0.0004
Body length (cm)	61.5 (56–65)	90.5 (69.6–105.0)	0.0004
Atrial septal defect	2	5	
Ventricular septal defect	4	4	
Complete atrioventricular canal	3	5	
Aortic stenosis	2	5	
Pulmonary stenosis	1	1	
Single ventricle	2	1	
Hypoplastic left heart syndrome	3	0	
Tetralogy of Fallot	2	4	
Double-outlet right ventricle	2	0	
Transposition of the great arteries	1	0	
Tricuspid atresia	1	0	
Total anomalous pulmonary venous return	1	1	
CPB time (min)	134 (103–182)	110 (85–136)	0.0637
Cross-clamp time (min)	44 (0–61)	42 (18–53)	0.8688

ethics committee of both hospitals. Informed written consent was obtained from the parents of each child.

The study included 50 consecutive patients in both centers (the parents of 2 children refused to participate in the study). As part of routine clinical care, all children weighing more than 7 kg received no steroids. Children weighing ≤ 7 kg received steroids into the priming solution of the CPB circuit at one center but not at the other. Accordingly, patients were grouped in a nonsteroid group and a steroid group (Table 1). During the study, only infants older than 3 months of age were included because of the known immaturity of the immune system in younger infants. All patients were operated on by the same two surgeons.

Cardiovascular function was assessed by the number and dosage of inotropic drugs used during the first 24 hours after CPB as well as the total duration of inotropic therapy. Postoperative inotropic support was done according to age-adapted reference values for blood pressure and clinical variables (i.e., skin perfusion and urine output) using dopamine, dobutamine, milrinone, adrenaline, or (rarely) noradrenaline, either as a single drug or in combination. In order to quantify the inotropic drugs used during the first 24 hours after CPB, a score was created with the following items: dopamine (dobutamine) ≤ 5 μg/kg/min = 1, dopamine (dobutamine) > 5 μg/kg/min = 2, milrinone ≤ 0.4 μg/kg/min = 1, milrinone > 0.4 μg/kg/min = 2, (nor-)epinephrine ≤ 0.1 μg/kg/min = 1, and (nor-)epinephrine > 0.1 μg/kg/min = 2. Prescription of the drugs was done by a team of intensive care physicians who were unaware of the laboratory results obtained for research purpose.

Postoperatively, patients were ventilated (Draeger Evita IV, Luebeck, Germany) using biphasic positive airway pressure mode. The fraction of inspired oxygen was adjusted to maintain an arterial oxygen tension of 10 kPa or greater. Respiratory function was determined as the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) calculated 24 hours after the end of CPB and the total duration of mechanical ventilation. The ratio PaO_2/FiO_2 was only used in patients during the second part of the study, when repair of cardiac lesion resulted in complete separation of pulmonary and systemic circulation in all cases. Mechanical ventilation was discontinued according to a standard weaning protocol, which is followed for all patients before extubation. Arterial blood samples for cytokine assays were collected from each patient before and 2 hours after CPB. Blood samples were immediately centrifuged and the plasma stored at −70°C until analysis.

CPB Management

The extracorporeal circuit (ECC) consisted of a roller pump, cardiotomy reservoir, tubing set, and oxygenator (Dideco, Mirandola, Italy). In both hospitals, the circuit was primed with a mixture of red blood cell concentrate, human albumine, sodium bicarbonate (8.4%), mannitol (20%), magnesium chloride, aprotinin (Bayer, Leverkusen, Germany), and heparin (Roche Pharma, Grenzach, Switzerland). Aprotinin was used in all patients in the same dosage of 50,000 U/kg. However, in Zurich, patients weighing less than 7 kg received 30 mg/kg prednisolone (Ultracorten H, Novartis Pharma, Basel, Switzerland) into the priming solution of CPB immediately before the start of CPB, whereas in children weighing more than 7 kg no steroids were added. In Berne, none of the patients received steroids. Cardioplegia solutions were the standard Buckberg potassium-based solutions mixed with blood in a ratio of 4:1 (blood:cardioplegia). CPB was conducted in mild hypothermia (32°C) with flow rates between 2.4 and 2.8 L/min/m^2. Ultrafiltration was performed in all patients in a standardized manner during the rewarming period using a blood concentrator (20 ml per minute resulting in a volume of 600 ± 200 ml). Heparin was neutralized with protaminhydrochloride (ICN Pharmaceuticals, Frankfurt, Germany) after the end of CPB.

Plasma Levels of IL-8

Concentrations of IL-8 were measured with a commercial enzyme-linked immunosorbent assay kit (Quantikine, R&D Systems) according to the manufacturer's recommendations.

Statistical Analysis

Data are expressed as the median value and interquartile range. Two-tailed tests were used for all statistical comparisons. Statistical significance was declared when $p < 0.05$. Comparisons between

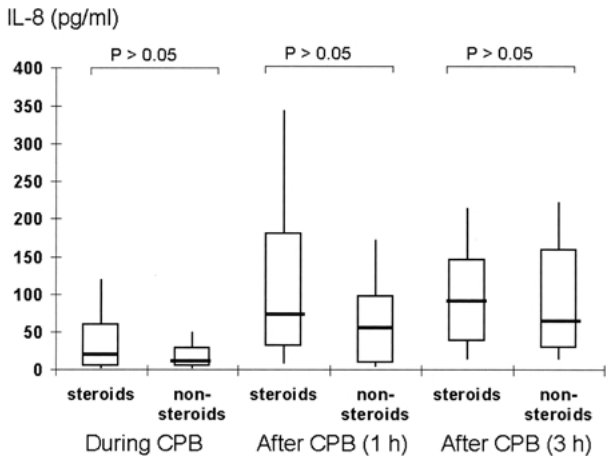

Fig. 1. Plasma levels of interleukin-8 during cardiopulmonary bypass (*CPB*), 1 hour after CPB, and 3 hours after CPB in patients treated in Zurich with or without steroids. The box and whisker plots show the median (*horizontal lines*), interquartile ranges (*bars*), and the extremes.

patients with and without steroid therapy with respect to clinical variables were done using the Mann–Whitney *U*-test. Analysis of the data at the different time points was performed using an analysis of variance for repeated measurements. Correlations between continuous variables were assessed using Spearman's rho correlation coefficient.

Results

Inflammatory Reaction after CPB

Plasma concentrations of IL-8 before CPB were less than 10 pg/ml in all patients and elevated during as well as 1 and 3 hours after CPB ($p < 0.001$) (Fig. 1). There was a correlation between levels of IL-8 1 hour after CPB and the CPB time ($r = 0.62$, $p < 0.001$). The median duration of CPB in patients treated with steroids was 134 minutes compared with 110 minutes in the nonsteroid group (Table 1). Furthermore, CPB time and aortic cross-clamp time in patients treated in both centers were comparable, demonstrating no statistically significant differences (data not shown). In patients treated with or without steroids, no significant differences in plasma IL-8 levels were detectable 1 and 3 hours after CPB (Fig. 1). Again, no center effect could be detected and postoperative plasma levels of IL-8 at both centers were equal.

Twenty-four hours after CPB, total neutrophil cell (TNC) counts of infants were significantly increased compared to preoperative values interquartile. Postoperatively, median TNC counts in the steroid group were 8.4 g/L (range, 6.7–10.3) vs preoperative 2.7 g/L (1.8–5.4) ($p = 0.002$); TNC counts in the nonsteroid group were 8.5 g/L (5.2–9.5) postoperatively vs 4.2 g/L (2.5–6.4) preoperatively ($p = 0.004$), respectively. No statistically significant difference could be detected between the postoperative leukocyte counts of the steroid group and the nonsteroid group (Table 2) as well as between the leukocyte counts of both centers (data not shown). Median concentrations of CRP were lower in infants after administration of steroids; however, the difference was not statistically significant.

Clinical Outcome

Cardiac diagnosis in the steroid and nonsteroid groups was different due to the limitation of steroid treatment to infants weighing less than 7 kg. In order to compare patients with respect to the clinical outcome after steroid treatment, patients of both centers were matched regarding to age, weight, and cardiac diagnosis. In patients treated with or without steroids, CPB and aortic cross-clamp times were statistically not different: median CPB time in the steroid group was 124 minutes (range, 108–133) and in the nonsteroid group 99 minutes (range, 82–105) ($p = 0.0892$); median aortic cross-clamp time in the steroid group was 50 minutes (range, 22–60) and in the nonsteroid group 46 minutes (range, 32–51) ($p = 0.7338$).

Cardiovascular function 24 hours after CPB was similar in both groups. Median inotropic score reflecting the kind and dose of inotropic drugs used during the first 24 hours after CPB was 2.1 (range, 1.0–3.0) in the steroid group compared to 2.6 (range, 2.0–3.8) in the nonsteroid group ($p = 0.3826$) (Table 3). Moreover, the total duration of inotropic therapy was statistically not different in both groups: median duration in the steroid group was 79.9 hours (range, 57.5–99.3) and in the nonsteroid group 62.5 hours (range, 34.0–72.3) ($p = 0.1856$).

With respect to the respiratory function, the ratio of PaO_2/FiO_2 assessed at 24 hours after CPB was equal in both groups. The median duration of mechanical ventilation was 75.0 hours in the steroid group (range, 40.8–95.8) and in the nonsteroid group 58.0 hours (range, 29.3–93.8) ($p = 0.3443$).

Blood concentrations of lactate, glucose, and hematocrit levels were similar in both groups. Blood creatinine levels were significantly increased after CPB compared with values before CPB in both groups. In the steroid group, creatinine before CPB was 43.5 μmol/L (range, 40.5–49.3) compared to 50.5 μmol/L (range, 48.3–55.3) after CPB ($p = 0.0322$). In the nonsteroid group, creatinine increased from 45.0 μmol/L (range, 42.0–48.8) to 52.5 μmol/L (range, 44.8–59.8) ($p = 0.0039$). The postoperative increase in creatinine was similar in both groups ($p = 0.9719$). In each group, one patient died postoperatively due to severe cardiac failure.

Table 2. Indices of inflammation after CPB

	Steroid group (n = 24)	Nonsteroid group (n = 26)	p value
TNC (g/L) (24 hr)	8.4 (6.7–10.3)	8.5 (5.2–9.5)	0.6165
Monocytes (g/L) (24 hr)	0.9 (0.5–1.2)	0.8 (0.5–1.2)	0.9835
Lymphocytes (g/L) (24 hr)	1.7 (1.4–2.3)	1.8 (1.3–2.6)	0.7726
CRP (mg/L) (24 hr)	51.0 (33.0–105.5)	73.0 (55.0–117.5)	0.2211

CRP, C-reactive protein; TNC, total neutrophil cell count.

Table 3. Clinical outcome parameters 24 hours after CPB

	Steroid group (n = 10)	Nonsteroid group (n = 10)	p value
Inotropic score	2.1 (1.0–3.0)	2.6 (2.0–3.8)	0.3826
PaO_2/FiO_2 (mmHg)	266.5 (227–318)	267.5 (183–363)	0.8880
Lactate (mmol/L)	1.0 (0.8–1.6)	1.3 (1.1–1.9)	0.1039
Glucose (mmol/L)	7.0 (6.7–8.5)	5.6 (4.7–5.9)	0.6953
Creatinine (μmol/L)	50.5 (48.3–55.3)	52.5 (44.8–59.8)	0.9719
Hematocrit (%)	34.5 (33.3–36.0)	36.0 (30.5–39.0)	0.5566

PaO_2/FiO_2, ratio of arterial oxygen tension to fraction of inspired oxygen.

Discussion

After CPB in infants, there was an impairment of cardiovascular and respiratory function as well as laboratory signs of inflammation. Administration of steroids before CPB had no influence on clinical postoperative recovery and did not suppress the inflammatory response.

Preoperative administration of steroids has been suggested to suppress the inflammatory reaction induced by CPB. Administration of glucocorticoids prior to CPB may attenuate endotoxin release and complement activation [8, 27]. Prednisolone lowers post-CPB concentrations of the proinflammatory cytokines tumor necrosis factor-α, IL-6, and IL-8 and increases concentrations of the anti-inflammatory cytokines IL-10 and IL-1RA [15, 19]. Corticosteroids also attenuate post-CPB leukocyte activation, neutrophil adhesion molecule upregulation, and pulmonary neutrophil sequestration [8, 15, 18]. In the current study, laboratory indices of inflammation were similar in patients with and without steroid pretreatment. Increased inflammatory response with elevated levels of IL-8 was reported and confirmed in this study after increased duration of CPB time [13, 16]. Median CPB time in patients treated with or without steroids was approximately the same and the laboratory indices of inflammation were similar for both groups. Moreover, when patients were matched for age and cardiac diagnosis, the inflammatory reaction was the same irrespective of steroid therapy, as shown by the comparison of treatment at the two different cardiosurgery centers. The lack of a demonstrable immunosuppressive effect may be due to the dose and timing of steroids [20, 26]. Indeed, a recent study showed lower inflammatory mediator expression when combined pre- and intraoperative steroid administration was given compared to intraoperative treatment with methylprednisolone (30 mg/kg per dose) alone [23].

The clinical implications of corticosteroid use are not fully elucidated, and clear benefit is not yet demonstrated [3]. Moreover, two recent clinical investigations of steroid administration in adults demonstrated no benefit or even an adverse outcome after steroid administration [4, 9, 24]. However, in children, Schroeder et al. [23] demonstrated improved oxygen delivery in the first 24 hours after congenital heart surgery with combined pre- and intraoperative steroid administration, but no significant difference was shown between the length of mechanical ventilation and the inotropic support. In order to compare the clinical outcome of children after cardiac surgery, patients of two centers were matched with respect to cardiac diagnosis, weight, and age. Neither inotropic support nor respiratory function after CPB were improved in patients treated with steroids. Again, the lack of benefit of steroid therapy in our study may be due to the dosage and timing of steroid administration. Moreover, infants in the study by Schroeder et al. were younger than those in our study and the CPB time was much longer, inducing an increased inflammatory reaction compared with the current study. Bronicki et al. [1] used dexamethasone (1 mg/kg intravenously) in children prior to CPB and reported improved postoperative respiratory function and less inflammatory response (e.g., decreased levels of IL-6 and tumor necrosis factor-α) without affecting neutrophil cell counts. Noteworthy in this study, CPB time and aortic cross-clamp time were

comparable to those of the current study, suggesting that dexamethasone at 1 mg/kg intravenously may be superior to 30 mg/kg prednisolone given into the priming solution before CPB.

Glucocorticoids are antianabolic agents that result in decreased synthesis of new protein, attenuation of immunity, and impairment of insulin action. In our study, blood glucose concentrations 24 hours after CPB were not different in patients treated with or without steroids. Moreover, none of our patients experienced septic complications.

The lack of benefit of steroid treatment in our study may be due to the less damaging effect of CPB components (e.g., the oxygenator causing less inflammation). Equipment and conduction of CPB were comparable in both centers and the main operative data, CPB time and aortic cross-clamp time, were similar. The majority of the infants had a favorable course after heart surgery. Perhaps another spectrum of operations or a different management of CPB would have caused more inflammatory reaction and thereby steroid administration would have demonstrated a more powerful immunosuppressive effect. An important shortcoming of our study is the fact that it is not a randomized, double-blind study. Indeed, steroids were given in one unit but not in the other. However, the clinicians responsible for the treatment of the children in both units were not informed about the results of the laboratory parameters of inflammation, and therapy with inotropic drugs, as well as mechanical ventilation, was done according to the same guidelines. Moreover, this is a noncommercial study and there is no conflict of interest.

In conclusion, in this group of infants older than 3 months of age, administration of steroids did not show a significant impact on the clinical outcome and the degree of the inflammatory response following cardiac surgery. The lack of suppression of the inflammatory reaction may be due to the dose and timing of steroid administration, the lower inflammatory reaction in patients with shorter time on CPB and less severe operative trauma, or an age older than 3 months at the time of surgery.

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