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Original Article

# Lung Injury After Neonatal Congenital Cardiac Surgery Is Mild and Modifiable by Corticosteroids

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*Objectives:* The present study was performed to determine whether lung injury manifests as lung edema in neonates after congenital cardiac surgery and whether a stress-dose corticosteroid (SDC) regimen attenuates postoperative lung injury in neonates after congenital cardiac surgery.

*Design:* A supplementary report of a randomized, double-blinded, placebo-controlled clinical trial.

*Setting:* A pediatric tertiary university hospital.

*Participants:* Forty neonates (age ≤28 days) undergoing congenital cardiac surgery with cardiopulmonary bypass.

*Interventions:* After anesthesia induction, patients were assigned randomly to receive intravenously either 2 mg/kg methylprednisolone or placebo b, which was followed by hydrocortisone or placebo bolus six hours after weaning from CPB for five days as follows: 0.2 mg/kg/h for 48 hours, 0.1 mg/kg/h for the next 48 hours, and 0.05 mg/kg/h for the following 24 hours.

*Measurements and Main Results:* The chest radiography lung edema score was lower in the SDC than in the placebo group on the first postoperative day (POD one) ($p = 0.03$) and on PODs two and three ($p = 0.03$). Furthermore, a modest increase in the edema score of 0.9 was noted in the placebo group, whereas the edema score remained at the preoperative level in the SDC group. Postoperative dynamic respiratory system compliance was higher in the SDC group until POD three ($p < 0.01$). However, postoperative oxygenation; length of mechanical ventilation; and tracheal aspirate biomarkers of inflammation and oxidative stress, namely interleukin-6, interleukin-8, resistin, and 8-isoprostane, showed no differences between the groups.

*Conclusions:* The SDC regimen reduced the development of mild and likely clinically insignificant radiographic lung edema and improved postoperative dynamic respiratory system compliance without adverse events, but it failed to improve postoperative oxygenation and length of mechanical ventilation.



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*Key Words:* lung injury; infant; glucocorticoid; congenital heart defect; pulmonary injury; pulmonary edema; cardiac surgery

AFTER CARDIAC surgery with cardiopulmonary bypass (CPB), the release of various inflammatory mediators and a lung ischemia-reperfusion process may lead to lung injury and lung edema.[1,2] However, more recently, very few patients tend to develop severe lung injury, and reperfusion lung edema mostly is a subclinical and self-limited condition.[3,4]

After pediatric and neonatal congenital cardiac surgery, systemic corticosteroid administration can decrease the systemic inflammatory reaction, but no significant effect on major clinical outcomes, such as mortality, have been demonstrated.[5-8] The authors' previous study in neonates showed that perioperative intravenous low-dose methylprednisolone (MP) bolus with postoperative stress-dose corticosteroid (SDC) decreased the systemic inflammatory response, stabilized hemodynamics, improved ventricular function, and did not suppress the hypothalamic-pituitary axis after neonatal congenital cardiac surgery with CPB.[8] In children, a combination of preoperative intravenous corticosteroid and intraoperative corticosteroid in CPB prime has improved postoperative oxygen delivery after congenital cardiac surgery with CPB.[9,10] However, postoperative inhaled corticosteroids have not affected the pulmonary inflammatory response assessed by cytokine concentrations in the lung lavage, pulmonary mechanics, or oxygenation.[11] In neonates, the effects of corticosteroids on postoperative pulmonary impairment remain unknown.

To supplement the authors' previously published randomized, double-blinded, placebo-controlled trial,[8] they aimed to evaluate whether neonatal cardiac surgery with CPB induces lung injury and whether SDC treatment prevents postoperative lung injury. The authors hypothesized that SDC treatment in neonates would reduce the risk for postoperative edema, inflammation, and ischemia-reperfusion injury of the lungs and improve postoperative lung function.

## Methods

### *Patients and Study Design*

This study comprised 40 neonates (age ≤28 days) undergoing congenital cardiac surgery with CPB between April 2012 and October 2014 at Children's Hospital, Helsinki University Hospital. The institution's Ethics Committee and the Finnish Medicines Agency approved the study protocol, and parents prospectively provided written informed consent. The study was registered in the European Union Drug Regulating Authorities Clinical Trials database (Eudra-CT 2011-005239-14).

The exclusion criteria for patients were prematurity (gestational age <36 weeks), chromosomal abnormalities, administration of corticosteroids before surgery, the need for high preoperative inotropic support, pulmonary malformation, and preoperative acute respiratory symptoms.[8] Fifty-one patients were eligible for the study, but nine patients were excluded because of parental refusal and two according to exclusion criteria. Study patients were randomly assigned to receive either 2 mg/kg MP or placebo (saline) bolus intravenously after the induction of anesthesia, according to a previously published protocol.[8] Six hours after weaning from CPB, the intervention group also received a hydrocortisone (HC) infusion of 0.2 mg/kg/h for 48 hours, 0.1 mg/kg/h for the next 48 hours, and 0.05 mg/kg/h for the following 24 hours. The placebo group received a saline infusion for five days similar to the intervention group. A pharmacist not involved in the patients' care prepared the study drugs. All clinical and study personnel were blinded to the treatment allocation until the study closed.

As reported in the primary report of the randomized clinical trial (RCT), nosocomial infections, elevated blood glucose levels (>10 mmol/L), and arrhythmias were considered adverse events potentially related to corticosteroid use.[8] To evaluate the function of the hypothalamic-pituitary-adrenal axis, the adrenocorticotropic hormone stimulation test was performed on the morning following discontinuation of the study drug. Adrenal insufficiency was defined as a baseline cortisol level <5 μg/dL or an increase of <16 μg/dL in the post-adrenocorticotropic hormone simulation level.

### *Intraoperative and Postoperative Management*

Three experienced cardiac surgeons performed the procedures. Balanced general anesthesia, CPB management, vasoactive support, and myocardial protection followed the same protocol as previously described.[8,12] All study patients were intubated with a cuffed endotracheal tube. Delayed sternal closure to prevent cardiac compression and hemodynamic instability was at the surgeon's discretion. Neonates with preoperative pulmonary hypertension typically received (iNO) after surgery. Postoperatively, in the pediatric intensive care unit (PICU), all patients were mechanically normoventilated with pressure-controlled synchronized intermittent mandatory ventilation by the SERVO-i ventilator (Maquet, Rastatt, Germany). The patients were extubated according to the clinician's decision, typically when the patient was under minimal sedation; breathed spontaneously with only minimal positive airway pressure support by the ventilator; and had stable hemodynamics with only moderate hemodynamic support with milrinone, norepinephrine, or epinephrine.

### *Chest Radiography*

Chest radiography (CXR) was taken preoperatively, early postoperatively (two-four hours after surgery), and on the first postoperative day (POD one) for all study patients, and from POD two-to-POD five based on clinical reasoning. A pediatric radiologist (L.M.), blinded to all clinical data, interpreted CXRs according to a pulmonary edema scoring system

adapted from the scoring method published by Maskatia et al. in 2012 and described in detail in a previous study by the authors of the present study.[13,14] Briefly, three bilateral areas of the CXRs were scored for lung edema on a four-step scale (0 = normal lung, 1 = minimal opacity not obscuring lung vessels, 2 = opacity partially obscuring lung vessels, 3 = opacity totally obscuring lung vessels). For each CXR, a mean lung edema score was calculated. If a patient had a CXR taken on both PODs two and three or on both PODs four and five, these two CXR lung edema scores were averaged and included in the analyses. An increase in the CXR edema score of two or more by POD one was used to define postoperative lung injury, as previously described.[14]

### *Measurements of Pulmonary Mechanics and Oxygenation*

Expiratory dynamic respiratory system compliance (Crs) was calculated automatically by the SERVO-i ventilator for each breath as follows[15]:

$$\text{dynamic Crs} = \frac{\text{expiratory tidal volume}}{\text{end inspiratory pressure} - \text{positive end expiratory pressure (PEEP)}}$$

Postoperative oxygenation was assessed with the oxygenation index (OI) and the ratio of partial pressure of arterial oxygen ($PaO_2$) and fraction of inspired oxygen ($FIO_2$). OI was calculated as follows:

$$= \frac{\textit{Mean airway pressure (MAP) x FiO2} \times 100}{(PaO2)}$$

Patients with postoperative right-to-left shunting (n = eight) were excluded from oxygenation analyses as a result of possible hypoxemia caused by shunting. Dynamic Crs, OI, and the ratio of $PaO_2$ and $FiO_2$ were recorded in two-minute intervals when the patient was mechanically ventilated. For analyses, an average value of the first six postoperative hours (considered as the early postoperative period), the average from then until noon at POD one, and then the average value of every 24-hour period until POD five were used.

### *Tracheal Aspirate and Plasma Sample Processing*

Tracheal aspirate (TA) samples were collected with instillation of 1 mL of 0.9% saline four-to-six, 24, 48, and 72 hours postoperatively from 22 patients until extubation. The sample was placed immediately at −20°C for ≤36 hours and then at −70°C until analyzed. TA samples were centrifuged at 4°C, 300 g for 10 minutes, supernatants were collected, and total protein concentration of the pellet was measured with the Bradford assay Supernatants were centrifuged for another ten minutes at 4°C, 16,000 g and stored at −70°C until analyzed. To measure concentrations of the proinflammatory cytokines interleukin 6 (IL-6), IL-8, and resistin, as well as 8-isoprostane, a marker of oxidative stress, previously published methods from the authors' laboratory were applied.[16] Enzyme-linked immunosorbent assays were performed using reagents from R&D Systems Europe Ltd, Abingdon, UK (resistin and IL-8); eBioscience Inc, San Diego, CA (IL-6); and Cayman Chemical, Ann Arbor, MI (8-isoprostane). The detection limits and coefficients of variation were 0.2 pg/mL and 5.4% for IL-6, 7.8 pg/mL and 4.4% for IL-8, 7.8 pg/mL and 6.0% for resistin, and 0.8 pg/mL and 7.8% for 8-isoprostane. The concentrations of IL-6, IL-8, and 8-isoprostane were reported as pg/mg of protein and resistin as ng/mg of protein.

Blood was collected from patients at anesthesia induction before study drug administration; five minutes and six hours after weaning from CPB; and on PODs one, two, and three. Storage of samples and analysis of IL-6, IL-10, and C-reactive protein previously were described .[6,8]

### *Statistics*

Power analyses for pulmonary measures used in the present study were based on the authors' previous data.[13,15] For each group, 18 patients were required to demonstrate a 40% difference in CXR lung edema (CXR LE) scoring, 19 patients were required to demonstrate a 20% difference in dynamic Crs, and 75 patients were required to demonstrate a 40% difference in OI ($\alpha = 0.05$, $1\text{-}\beta = 0.8$ for all).

In two of the placebo-group patients, because of high inotropic support, study infusion was stopped and HC then started (PODs one and four). The plasma IL-6 and TA inflammatory marker levels of these two patients were omitted from analyses after cessation of the study drug, but all other data were included in the intention-to-treat analysis.

Variables on a qualitative scale are presented as number with percentages and comparisons between groups by the chi-square test. Variables on a continuous scale were described as mean ± standard deviation or median with interquartile range, and the comparisons between groups were analyzed with Student *t* or Mann-Whitney *U* test, as appropriate. Repeated measurements were compared using the Friedman and Wilcoxon tests. Associations were examined with Spearman's test. For all statistical analyses, a p value $\leq 0.05$ was considered to be significant. Statistical analyses were performed with SPSS 24.0 (IBM Corp, Armonk, NY) and Prism 8.0 (GraphPad Software, La Jolla, CA).

## Results

### *Demographics and Clinical Outcome*

Both the SDC and placebo groups were similar in baseline demographics, complexity of surgery, and perioperative factors (Table 1). Two patients in the placebo group died. One patient died ten days after truncus arteriosus repair followed by extracorporeal membrane oxygenation, and another patient died because of multiorgan failure with acute respiratory distress syndrome (ARDS) 25 days after correction of tetralogy of Fallot with hypoplastic pulmonary arteries. As reported previously, length of PICU stay was similar in both groups. The sternum was left open for a longer period in the placebo group than in the SDC group (p = 0.02) (Table 2). Occurrence of focal adverse events potentially related to corticosteroids

Table 1
Patient Demographics and Preoperative and Perioperative Data

| | N = 40 | Stress-Dose Corticosteroid n = 20 | Placebo n = 20 | p Value* |
|---|---|---|---|---|
| Demographics | | | | |
| Age, d | 7 (5-11) | 8 (5-11) | 7 (5-11) | 0.47 |
| Gestational age, wk | 39.7 (39.0-40.3) | 39.1 (38.6-40.0) | 40.0 (39.0-40.4) | 0.16 |
| Male sex | 29 (73%) | 15 (75%) | 14 (70%) | 0.72 |
| Weight, kg | 3.45 (3.10-3.88) | 3.37 (3.03-3.88) | 3.50 (3.10-3.91) | 0.76 |
| Preoperative ventilation | | | | |
| Mechanical ventilation | 4 (10%) | 3 (15%) | 1 (5%) | 0.59 |
| Nasal CPAP | 6 (15%) | 3 (15%) | 3 (15%) | 1.00 |
| Perioperative data | | | | |
| CPB time, min | 169 (145-209) | 175 (152-225) | 167 (121-197) | 0.28 |
| ACC time, min | 90 (75-128) | 98 (80-131) | 86 (53-125) | 0.27 |
| ACP | 17 (43%) | 9 (45%) | 8 (40%) | 0.75 |
| ACP time, min | 50 (39-63) | 55 (41-71) | 48 (36-53) | 0.19 |
| Lowest temperature, ˚C | 24.9 (23.4-28.9) | 25 (23-28) | 25 (23-29) | 0.95 |
| Surgery | | | | |
| RACHS-1 score | 4 (3-4) | 4 (3-6) | 3 (3-4) | 0.34 |
| Arterial switch surgery | 18 (45%) | 10 (50%) | 8 (40%) | 1.00 |
| Hypoplastic aortic arch reconstruction | 7 (18%) | 3 (15%) | 4 (20%) | 0.43 |
| Norwood | 8 (20%) | 5 (25%) | 3 (15%) | 0.69 |
| TAPVD repair | 3 (8%) | 1 (5%) | 2 (10%) | 0.55 |
| Tetralogy of Fallot repair | 1 (2.5%) | 0 (0%) | 1 (5%) | 0.31 |
| Truncus arteriosus repair | 1 (2.5%) | 0 (0%) | 1 (5%) | 0.31 |
| Ventricular septal defect repair | 2 (5%) | 1 (5%) | 1 (5%) | 1.00 |

NOTE. Data are expressed as n (%) or median (interquartile range), as appropriate.
Abbreviations: ACC, aortic cross-clamp; ACP, antegrade cerebral perfusion; CPAP, continuous positive airway pressure; CPB, cardiopulmonary bypass; RACHS-1, risk adjustment in congenital heart surgery; TAPVD, total anomalous pulmonary venous drainage.
* Comparisons between stress-dose corticosteroid and placebo group.

showed no difference between the groups (see Table 2). Importantly, the SDC regimen did not cause suppression of the hypothalamic-pituitary-adrenal axis.[8]

### *Radiographic Lung Edema*

One patient in the placebo group had an increase in the CXR LE score of 2 after arterial switch surgery by POD one. In the placebo group, the CXR LE score increased from preoperative to early postoperative and further to POD one and was higher than in the SDC group on PODs one-to-three (Fig 1).

### *Postoperative Pulmonary Mechanics, Oxygenation, and Pulmonary Outcome*

Dynamic Crs was higher in the SDC group from early postoperative period to POD three (Fig 2). Dynamic Crs showed a negative correlation with the CXR LE score on POD one ($r = -0.58$, $n = 26$; $p = 0.002$) and on POD three ($r = -0.61$, $n = 22$; $p = 0.003$), but not at other measurement points.

Postoperative oxygenation, which was assessed with OI and the ratio of $PaO_2$ and $FIO_2$, was similar in both groups (see Table 2). No difference in initiation of iNO was noted, but iNO treatment was continued longer in the placebo group ($p = 0.03$) (see Table 2). As reported previously, length of mechanical ventilation was similar in both groups (see Table 2).[8]

### *Inflammatory Response in Plasma and Tracheal Aspirates*

As reported in the RCT primary report, the SDC group, compared with the placebo group, had lower proinflammatory cytokine IL-6 levels in the plasma six hours postoperatively and on PODs one and two and had higher IL-10 levels five minutes after weaning from CPB.[8] Furthermore, C-reactive protein concentrations were higher in the placebo group from PODs one-to-five.[8] IL-6 levels in the plasma correlated with IL-6 levels in TA on POD two ($r = 0.64$, $n = 19$; $p = 0.003$), and a similar but nonsignificant trend was found four-to-six hours postoperatively ($r = 0.44$, $n = 19$; $p = 0.06$) and on POD one ($r = 0.40$, $n = 18$; $p = 0.10$). No significant differences were observed in TA levels of IL-6, IL-8, resistin, and 8-iso-prostane between the groups (Table 3).

## Discussion

This study demonstrated that perioperative intravenous low-dose MP bolus, followed by stress-dose HC infusion for five postoperative days, reduced radiographic lung edema scoring and improved dynamic Crs compared with placebo treatment in neonates. However, no differences in length of mechanical ventilation, oxygenation, or TA markers of inflammation and oxidative stress occurred. To the best of the authors' knowledge, this was the first RCT evaluating the effects of perioperative corticosteroids on pulmonary injury after congenital cardiac surgery with CPB in neonates.[9,10] Furthermore, the

Table 2
General Clinical and Pulmonary Outcome Data

| | N = 40 | Stress-Dose Corticosteroid n = 20 | Placebo n = 20 | p Value* |
|---|---|---|---|---|
| Length of PICU stay, d | 8 (5-10) | 7 (5-9) | 9 (5-11) | 0.31 |
| Mechanical ventilation, d | 5 (4-8) | 5 (4-6) | 6 (3-10) | 0.28 |
| Delayed sternal closure | 30 (73%) | 15 (75%) | 14 (70%) | 0.41 |
| Sternum open, d | 3 (3-5) | 3 (2-4) | 5 (3-6) | 0.02 |
| Death in PICU | 2 (5%) | 0 (0%) | 2 (10%) | 0.15 |
| Fluid balance at 12:00 on POD 1, mL/kg | 56 (−33 to 184) | 42 (−67 to 156) | 62 (−3 to 199) | 0.52 |
| Adverse events | | | | |
| Insulin administration | 14 (35%) | 9 (45%) | 5 (25%) | 0.33 |
| Low baseline cortisol level | 37 (93%) | 19 (95%) | 18 (90%) | 1.0 |
| Subnormal response to ACTH test | 10 (25%) | 7 (18%) | 3 (15%) | 0.11 |
| Wound infection | 5 (13%) | 3 (15%) | 2 (10%) | 0.63 |
| Septic blood culture-positive infection | 2 (5%) | 0 (0%) | 2 (10%) | 0.31 |
| Perioperative or postoperative arrhythmias | 22 (55%) | 11 (55%) | 11 (55%) | 1.0 |
| Oxygenation index† | | | | |
| 6 h postoperatively | 2.2 (1.6-2.7) | 2.2 (1.5-2.9) | 2.2 (1.7-2.6) | 0.78 |
| POD 1 | 2.6 (1.9-3.6) | 2.7 (1.6-3.6) | 2.5 (2.0-3.7) | 0.66 |
| POD 2 | 2.6 (1.7-3.7) | 2.2 (1.7-3.2) | 2.7 (1.9-4.1) | 0.51 |
| POD 3 | 2.2 (1.7-3.0) | 2.5 (1.6-3.5) | 2.2 (2.0-2.7) | 0.86 |
| POD 4 | 2.5 (1.8-3.7) | 2.4 (1.6-3.7) | 2.5 (1.9-3.6) | 0.62 |
| POD 5 | 2.0 (1.7-3.2) | 2.4 (1.8-4.0) | 2.0 (1.5-3.2) | 0.37 |
| $PaO_2/FiO_2$ ratio† | | | | |
| 6 h postoperatively | 315 (232-416) | 290 (226-541) | 318 (255-386) | 0.75 |
| POD 1 | 268 (186-326) | 275 (186-382) | 260 (175-302) | 0.44 |
| POD 2 | 240 (200-335) | 279 (203-337) | 235 (190-331) | 0.48 |
| POD 3 | 269 (224-354) | 239 (198-377) | 283 (250-345) | 0.42 |
| POD 4 | 249 (193-349) | 259 (187-364) | 249 (210-342) | 0.94 |
| POD 5 | 281 (189-358) | 235 (151-326) | 302 (235-363) | 0.37 |
| iNO during PICU stay | 14 (35%) | 8 (40%) | 6 (30%) | 0.51 |
| Length of iNO treatment, d | 6 (4-8) | 5 (3-6) | 9 (6-10) | 0.03 |

NOTE. Data are expressed as n (%) or median (IQR), as appropriate.
Abbreviations: ACTH, adrenocorticotropic hormone; $FiO_2$, inspired oxygen fraction; iNO, inhaled nitric oxide; $PaO_2$, partial pressure of oxygen in arterial blood; PICU, pediatric intensive care unit; POD postoperative.
* Comparisons between stress-dose corticosteroid and placebo group.
† Patients with postoperative right-to-left shunting were excluded from oxygenation analyses (4 patients in SDC group and 4 in placebo group).

importance of the study's observations was underscored by the particular susceptibility of neonatal patients to postoperative complications after cardiac surgery.[17]

The CXR LE score increased slightly in the placebo group during the first postoperative days; whereas in the SDC group, no sequential variation was noted. A similar increase was detected in the CXR LE score after congenital cardiac surgery with CPB in the authors' previous study, which also used lung ultrasound to assess lung edema.[18] Despite the difference between the groups, radiographically evaluated lung injury was mild in both the SDC and placebo groups, and only one patient in the placebo group showed an increase in the CXR LE score consistent with postoperative lung injury. These days, few patients develop severe lung injury, and reperfusion lung edema mostly is a subclinical and self-limited condition.[3,4] Similarly, in the present study, none of the patients developed ARDS early postoperatively, and only one patient later developed multiorgan failure with ARDS. An accurate method to measure lung edema and to detect postoperative lung injury after congenital cardiac surgery is lacking. Previously, the CXR LE score was used successfully to detect lung injury after the unifocalization procedure in tetralogy of Fallot patients with pulmonary atresia and major aortopulmonary collateral arteries.[14] Clinically, CXRs are used, although lung ultrasound has shown some potential in measurement of lung edema and prognosis of intensive care unit stay length after congenital cardiac surgery.[18,19]

The improvement in dynamic Crs during the first PODs in the patients who received the SDC regimen was in line with previous studies on adults and animals, whereas a previous pediatric study failed to demonstrate an effect of postoperative inhaled corticosteroids on dynamic Crs.[11,20,21]

Intravenous corticosteroids have had differing effects on postoperative oxygenation after cardiac surgery with CPB in adults.[22,23] In children, Schroeder et al. showed that combining preoperative intravenous corticosteroid and intraoperative corticosteroid in CPB prime improved oxygen delivery.[10] However, intraoperative corticosteroid administration to CPB prime alone or postoperative corticosteroid inhalations in children have not improved oxygenation during the first POD after cardiac surgery with CPB.[9,11] Consistently, the presents study found no difference in postoperative oxygenation. However, this should be interpreted with caution because the study did not reach power to draw such conclusions. The initiation of

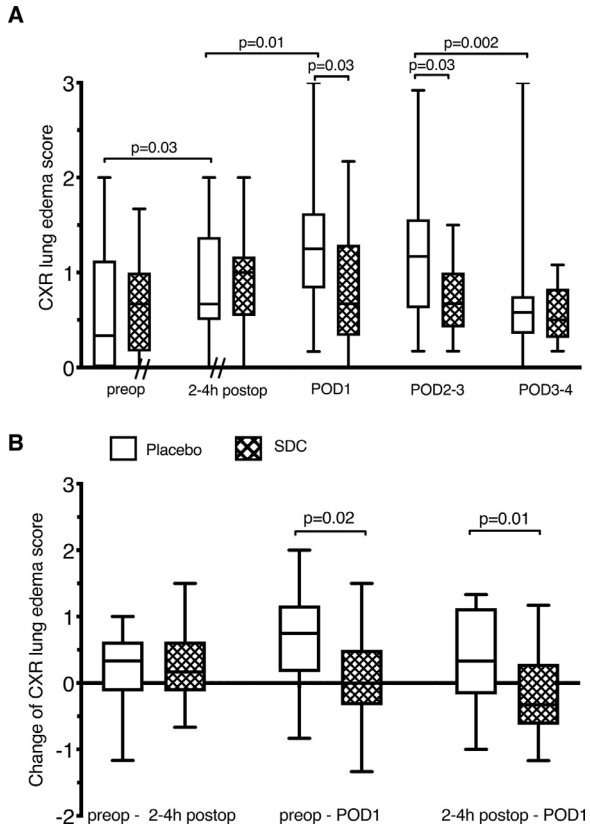


Fig 1. (A) Comparison of chest x-ray lung edema score from preoperative to the fourth-to-fifth postoperative days and between sequential postoperative days between stress-dose corticosteroid and placebo groups. (B) Comparison of chest x-ray lung edema score changes between stress-dose corticosteroid and placebo groups. *Boxes* indicate interquartile range with median line, and *whiskers* indicate minimum and maximum. Only comparisons with $p < 0.05$ are shown. CXR, chest x-ray lung edema; POD, postoperative day; SDC, stress-dose corticosteroid.

iNO treatment was similar in both groups, which may indicate that no significant difference in preoperative manifestation of clinical pulmonary hypertension occurred between the groups. However, iNO treatment was finished earlier in the SDC group. Because iNO is used to improve oxygenation, especially in patients with pulmonary hypertension or with subpulmonary ventricle failure, this finding may indicate that the placebo group had a more severe postoperative pulmonary course.[24]

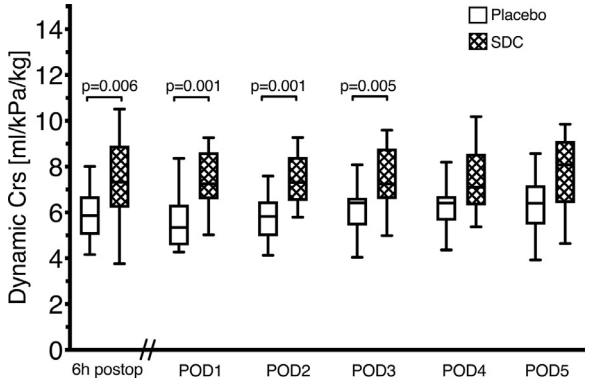


Fig 2. Comparison of dynamic respiratory system compliance from early postoperative period to fifth postoperative day between stress-dose corticosteroid and placebo groups. *Boxes* indicate interquartile range with median line, and *whiskers* indicate minimum and maximum. Only comparisons with $p < 0.05$ are shown. Crs, respiratory system compliance; POD, postoperative day; SDC, stress-dose corticosteroid.

Systemic steroid use has failed to reduce the length of mechanical ventilation after cardiac surgery in pediatric studies, including the present study.[7,8,25,26] Even though in an RCT on adult patients, high-dose dexamethasone helped shorten mechanical ventilation after cardiac surgery, the pediatric study cohorts may have been too small to answer this question.[27] Furthermore, in the present study, because postoperative lung edema was only mild and lung injury scarce, the SDC regimen may have lacked significant effect on major clinical outcomes. Although initiation of iNO treatment was similar in both groups, iNO treatment was finished earlier in the SDC group. Because iNO is used to improve oxygenation, especially in patients with pulmonary hypertension or with subpulmonary ventricle failure, this finding may indicate that the placebo group had a more severe postoperative pulmonary course.[24]

In adults, MP reduces postoperative proinflammatory cytokine levels and increases anti-inflammatory cytokine levels in bronchoalveolar lavage fluid samples collected after CPB and during thoracic surgery with one-lung ventilation.[20,28] In the present study's SDC group, TA markers of inflammation and oxidative stress were not lower than in the placebo group despite differences in clinical parameters assessing pulmonary injury. Contrary to the authors' previous results on adults demonstrating that plasma resistin levels increase after cardiac surgery with CPB and are associated with oxidative stress myocardial injury, TA resistin levels showed no significant postoperative increase.[16] Thus, it could be conjectured that current improved perfusion protocols cause only a modest lung injury, not readily detectable by biomarkers of inflammation, oxidative stress, and alveolar injury in TAs.[3]

The authors of the present study chose the dose, timing, and route of MP administration based on their previous studies in pediatric patients undergoing cardiac surgery.[6,12,29] In previous studies, high-dose MP treatment has been noted to induce a higher frequency of postoperative hyperglycemia.[12,29] Hyperglycemia in small children after cardiac surgeries has been associated with increased organ dysfunction, rate of infection, length of mechanical ventilation, length of PICU and hospital stay, and mortality rates.[30] Furthermore, a high dose of 30 mg/kg MP produced no beneficial anti-inflammatory effect compared with moderate doses of 2-to-5 mg/kg.[12,31] Moreover, the elimination half-life of MP is approximately two hours, which further underlines the importance of continuous postoperative HC infusion.[32] Importantly, the differences in corticosteroid dosages and administration routes may largely explain the difference between the present observations and previous studies measuring pulmonary injury after cardiac surgery with CPB in children.[9-11]

There were certain limitations to consider in this study, primarily the relatively small sample size from a single center. Second, the preoperative TA samples and dynamic Crs values

Table 3
Tracheal Aspirate Biomarker Concentrations

| | n =22 | Stress-Dose Corticosteroid n = 13 | Placebo n = 9 | p Value |
|---|---|---|---|---|
| IL-6, pg/protein mg | | | | |
| 6 h postoperatively | 818 (356-2,120) | 361 (283-2,121) | 1,006 (725-2,006) | 0.08 |
| POD 1 | 992 (279-1,583)* | 787 (277-1,380) | 1,199 (299-4,410) | 0.40 |
| POD 2 | 361 (167-1,218)* | 233 (85-698) | 906 (252-2,410) | 0.07 |
| POD 3 | 334 (125-692) | 263 (60-434) | 388 (134-1,793) | 0.24 |
| IL-8, pg/protein mg | | | | |
| 6 h postoperatively | 11,480 (5,580-29,460) | 10,440 (5,270-29,460) | 12,060 (10,550-48,153) | 0.46 |
| POD 1 | 20,875 (5,250-50,028) | 18,920 (4,855-34,750) | 59,050 (6,700-77,100) | 0.12 |
| POD 2 | 17,130 (5,360-32610) | 7,740 (4,165-27,172) | 21,580 (12,695-83,760)† | 0.17 |
| POD 3 | 11,530 (6,360-21,980) | 11,675 (4,152-20,630) | 11,530 (6,670-115,130)† | 0.56 |
| 8-Isoprostane, pg/protein mg | | | | |
| 6 h postoperatively | 167 (53-244)‡ | 127 (42-203) | 188 (67-320) | 0.48 |
| POD 1 | 83 (25-166)‡ | 57 (25-230) | 121 (34-166) | 0.82 |
| POD 2 | 98 (57-176)§ | 78 (62-149) | 140 (52-384)¶ | 0.48 |
| POD 3 | 52 (43-137)§ | 50 (41-85) | 111 (40-301)¶ | 0.38 |
| Resistin, ng/protein mg | | | | |
| 6 h postoperatively | 360 (168-617) | 360 (168-611) | 340 (130-756) | 0.93 |
| POD 1 | 867 (196-1,466) | 782 (153-1,448) | 1207 (230-1,500) | 0.48 |
| POD 2 | 989 (236-2,674) | 375 (190-2,730) | 1002 (468-3,106) | 0.41 |
| POD 3 | 602 (243-1,780) | 830 (206-17,80) | 526 (355-3,463) | 0.79 |

NOTE. Data are expressed as median (interquartile range), and comparisons between stress-dose corticosteroid and placebo groups were with Mann-Whitney *U* test.

Abbreviations: IL-6, interleukin 6; IL-8, interleukin 8; POD, postoperative day.

* IL-6 level decreased from postoperative days one-to-three in the whole study population (p = 0.018).

† IL-8 level decreased from postoperative days two-to-three in the placebo group (p = 0.028).

‡ Isoprostane-8 level decreased in the whole study population from early postoperative to postoperative day one (p = 0.008).

§ Isoprostane-8 level decreased in the whole study population from postoperative days two-to-three (p = 0.022).

¶ Isoprostane-8 level decreased in the placebo group from postoperative days two-to-three (p = 0.028).

were lacking, and the number of TA samples was limited because of clinical and logistic reasons. Third, the number of measurements of dynamic Crs and CXRs decreased after POD one because of early extubation and successful postoperative recovery, possibly diminishing the statistically significant results. Finally, the difference in dynamic Crs may not reflect Crs alone, but also airway resistance, which is affected by several factors, such as secretions and the length and diameter of the endotracheal tube.[15]

## Conclusions

In neonates undergoing cardiac surgery, perioperative intravenous corticosteroid, followed by five days of stress-dose hydrocortisone infusion, resulted in reduced accumulation of postoperative radiographic lung edema and enhanced postoperative dynamic Crs. However, radiographic lung edema was only mild, and no obvious effect on clinical outcome or tracheal aspirate markers of inflammation and oxidative stress occurred. The authors concluded that in today's era of exceptional neonatal cardiac surgery, perioperative administration of corticosteroids, together with postoperative SDC, may offer some benefit in terms of lung protection after cardiac surgery in neonates with no adverse events. Future studies with a larger study population are needed to assess the association of these findings and major clinical outcomes.[33]

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## Conflict of Interest

The authors have no conflict of interest.

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