Effect of Intraoperative Dexamethasone on Major Complications and Mortality Among Infants Undergoing Cardiac Surgery
The DECISION Randomized Clinical Trial

Vladimir Lomivorotov, MD, PhD; Igor Kornilov, MD, PhD; Vladimir Boboshko, MD, PhD; Vladimir Shmyrev, MD, PhD; Ilya Bondarenko, MD, PhD; Ilya Soynov, MD, PhD; Alexey Voytov, MD; Stanislav Polyanskih, MD; Oleg Strunin, MD, PhD; Alexander Bogachev-Prokophiev, MD, PhD; Giovanni Landoni, MD; Caetano Nigro Neto, MD, PhD; Gretel Oliveira Nicolau, MD; Leonardo Saurith Izquierdo, MD; Vinicius Nogueira Nascimento, MD; Zhang Wen, MD; Hu Renjie, MD; Zhang Haibo, MD, PhD; Vladlen Bazylev, MD, PhD; Mikhail Evdokimov, MD, PhD; Shahrijar Sulejmanov, MD; Aleksei Chernogrivov, MD, PhD; Dmitry Ponomarev, MD, PhD, MSc

IMPORTANCE Corticosteroids are widely used in pediatric cardiac surgery to blunt systemic inflammatory response and to reduce complications; nevertheless, their clinical efficacy is uncertain.

OBJECTIVE To determine whether intraoperative administration of dexamethasone is more effective than placebo for reducing major complications and mortality during pediatric cardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS The Intraoperative Dexamethasone in Pediatric Cardiac Surgery was an investigator-initiated, double-blind, multicenter randomized trial that involved 4 centers in China, Brazil, and Russia. A total of 394 infants younger than 12 months, undergoing cardiac surgery with cardiopulmonary bypass were enrolled from December 2015 to October 2018, with follow-up completed in November 2018.

INTERVENTIONS The dexamethasone group (n = 194) received 1 mg/kg of dexamethasone; the control group (n = 200) received an equivolume of 0.9% sodium chloride intravenously after anesthesia induction.

MAIN OUTCOMES AND MEASURES The primary endpoint was a composite of death, nonfatal myocardial infarction, need for extracorporeal membrane oxygenation, need for cardiopulmonary resuscitation, acute kidney injury, prolonged mechanical ventilation, or neurological complications within 30 days after surgery. There were 17 secondary end points, including the individual components of the primary end point, and duration of mechanical ventilation, inotropic index, intensive care unit stay, readmission to intensive care unit, and length of hospitalization.

RESULTS All of the 394 patients randomized (median age, 6 months; 47.2% boys) completed the trial. The primary end point occurred in 74 patients (38.1%) in the dexamethasone group vs 91 patients (45.5%) in the control group (absolute risk reduction, 7.4%; 95% CI, −0.8% to 15.3%; hazard ratio, 0.82; 95% CI, 0.60 to 1.10; P = .20). Of the 17 prespecified secondary end points, none showed a statistically significant difference between groups. Infections occurred in 4 patients (2.0%) in the dexamethasone group vs 3 patients (1.5%) in the control group.

CONCLUSIONS AND RELEVANCE Among infants younger than 12 months undergoing cardiac surgery with cardiopulmonary bypass, intraoperative administration of dexamethasone, compared with placebo, did not significantly reduce major complications and mortality at 30 days. However, the study may have been underpowered to detect a clinically important difference.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02615262


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Since 1998, there has been a significant reduction in mortality in pediatric patients undergoing cardiac surgery with cardiopulmonary bypass for congenital heart defects. Although the mortality dropped to approximately 3%, major complications remained between 30% and 40%. It has been widely recognized that the systemic inflammatory response triggered by cardiopulmonary bypass compromised organ function and has been associated with prolonged intensive care unit stay and hospitalization. Moreover, there was concern about adverse effects of corticosteroids, including the risk of infection and myocardial injury. Pasquali et al suggested that perioperative administration of corticosteroids was not associated with better perioperative outcomes and was strongly associated with an increased rate of infectious complications in low-risk pediatric patients undergoing cardiac surgery. Two large multicenter randomized clinical trials showed no benefit of corticosteroids administration in adult patients undergoing cardiopulmonary bypass with an increased risk of myocardial injury.

Even if there are no dedicated guidelines regarding corticosteroids administration for pediatric cardiac surgery, 54% of patients receive these drugs perioperatively. The Intraoperative Dexamethasone in Pediatric Cardiac Surgery, an investigator-initiated, double-blind, multicenter randomized clinical trial, aimed to test the hypothesis that intraoperative administration of dexamethasone was more effective than placebo for reducing major complications and mortality among pediatric patients undergoing cardiac surgery with cardiopulmonary bypass.

**Methods**

**Trial Design and Setting**

We performed this randomized, double-blind, placebo-controlled trial in 4 centers in Brazil, China, and Russia. The trial protocol was approved by the ethics committee at each site, and written informed consent was obtained from patients' legal representatives. The trial protocol, including the statistical analysis plan, available in Supplement 1. The trial design has been previously published.

Eligible patients were infants 12 months or younger, scheduled for elective cardiac surgery with cardiopulmonary bypass. Patients were excluded if they needed emergency surgery; had hypoplastic left heart syndrome; used of steroids or inotropes; had confirmed infection within 30 days, severe perinatal central nervous system damage, gestational age younger than 37 weeks, mechanical ventilation, or use of inotropes prior to surgery; or were participating in conflicting trials. Eligible patients were randomized in a 1:1 ratio by an independent biostatistician to receive either dexamethasone or placebo. The randomization was accomplished using an online randomization service (http://www.sealedenvelope.com). A permuted-block technique with block size chosen at random between 4 and 6 and concealed from investigators was used. To ensure balanced distribution, the randomization was stratified by center, sex, and age. Each center received a set of sequentially numbered sealed opaque envelopes containing treatment allocation, to be opened immediately before anesthesia induction.

The dexamethasone group received 1 mg/kg of dexamethasone; the control group, an equivalent of 0.9% sodium chloride. The 2 solutions, identical in appearance and volume, were prepared in a separate room by a dedicated staff member, not otherwise involved in the trial, and arrived into operation room in unmarked syringes. Both drugs were given intravenously immediately after anesthesia induction. Clinicians (anesthesiologists, perfusionists, intensivists), outcome assessors, and patients’ legal representatives were blinded to treatment allocation. The randomization code could be broken in case of suspected allergic reaction, aspiration, concern for airway edema, and cardiopulmonary resuscitation. Suspected allergy was defined as any adverse effect of a drug during or after anesthesia that manifested in rash, bronchospasm, or pulmonary hypertension crisis. In cardiac surgery, an allergic reaction to protamine sulfate is not uncommon and many clinicians resort to steroids to suppress the response. There was no limitation to use of any drug, with the exception of steroids. Open-label steroids could be administered only after randomization code break.

Treatment approaches and local protocols at participating centers were reviewed by the steering committee and reconciled before the commencement of the study. All centers had similar approaches to the indications for surgery, surgical technique, and perioperative management. Minor differences in therapy (eg, perioperative antibiotic prophylaxis) were deemed nonsignificant.

All patients received the best available care at each center. Similar anesthesia protocols based on sevoflurane and fentanyl were used in all the centers. Invasive blood pressure monitoring was performed using right radial or femoral artery. Cerebral near-infrared spectroscopy for noninvasive assessment of cerebral oxygenation was monitored throughout...
the procedure. Donor red blood cells, fresh frozen plasma, 20% albumin, sodium bicarbonate, mannitol, and heparin were used to prime the extracorporeal circuit. In all cases, ascending aorta and superior and inferior vena cava were cannulated. If necessary, left ventricular vent was placed through the right upper pulmonary vein. Cardiopulmonary bypass was performed with a flow of 150 mL/kg of body weight. Acid-base management was maintained using the pH stat strategy with a hematocrit goal of 30% during bypass. For myocardial protection during aortic cross-clamping, antegrade cardioplegia was administered (either Bretschneider's cardioplegic solution; [Custodiol HTK, Koehler Chemie] once, immediately after aortic cross-clamping, or cold-blood cardioplegia at 20-minute intervals). All centers used both modalities of cardioplegia. All used cardioplegic solutions did not contain any steroids. Some patients' operations were without the cardioplegia and aorta cross clamping with induced ventricular fibrillation (included in subgroup analysis). At the conclusion of surgery, all patients were transferred to the intensive care unit and their care managed according to standard practices at each center, with the exception of steroids, the use of which was strictly regulated.

Outcomes
The primary end point was a composite of death, nonfatal myocardial infarction, need for extracorporeal membrane oxygenation, cardiopulmonary resuscitation, acute kidney injury (at least stage “Injury” according to the pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease [pRIFLE] scale), prolonged mechanical ventilation (≥24 hours), and neurologic event (stroke, seizures, or coma). For the definition of the components of the primary end point, see eTable 1 in Supplement 2. The primary end point was met as soon as any of its components occurred.

Secondary end points were individual components of the composite end point and were the duration of mechanical ventilation, maximal vasoinotropic index during the first 24 hours after surgery, and vasoinotropic index greater than 10 for 24 hours or more at 5 for 48 hours after the operation; use of a pacemaker; blood loss; and number of transfused blood components in the first day after surgery; duration of stay in intensive care unit; readmission to intensive care unit; length of hospitalization; and reason for code break, if applicable. Additionally, a post hoc analysis of blood glucose was carried out.

An infection (suspected or proven) was considered as an adverse event. For all end points and adverse events, which are detailed in eTables 1 through 3 in Supplement 2, the follow-up period was 30 days after enrollment or the end of hospitalization if it was longer than 30 days. The follow-up contact with the patient representative was made via phone call.

Statistical Methods
Sample Size Estimation
Based on published evidence and on local experience, we expected an absolute risk of the primary end point of 40% in the control group. Therefore, 306 patients would be sufficient to detect an absolute risk difference of 15% for the primary end point with a probability of type I error of 5% and power of 80%.

The choice of minimally clinically important difference was based on a consensus between clinical experts and local ethics committees at all 4 centers. To compensate for incomplete observations and protocol violations, the estimated sample size was increased by 25%. The resulting total sample size was therefore 384 patients (192 patients in each group).

Prespecified Primary, Secondary, and Subgroup Analyses
All randomized patients were included in the analysis. For the primary treatment comparison, a time-to-first-event analysis was used. Periods at risk were defined in days for each participant, starting the day of randomization and ending with an event or censoring (withdrawal, loss to follow-up, or end of the study period). The survival times were estimated using the Kaplan-Meier estimator and compared using log-rank test. Cox regression modeling was used to derive relative risks, expressed in terms of hazard ratios (HRs) and associated 95% CIs. The Cox model was also used to evaluate consistency of treatment effect by testing for interaction between treatment strategy and prespecified baseline and clinical characteristics (sex, age ≤30 days, use of antegrade cerebral perfusion, circulatory arrest, left-to-right intracardiac shunting, surgery on fibrillating heart). Additionally, a post hoc test for interaction between treatment and site (as a categorical variable with 4 levels) was performed. The constant relative hazard assumption was investigated by correlating scaled Schoenfeld residuals with a suitable transformation of time, along with a global test for the model as a whole. The assumption of linearity between log-hazard ratio and a covariate was assessed graphically by plotting Martingale residuals against the covariate. Based on the above methods, the assumptions of Cox proportional hazards model were deemed plausible.

For between-group comparisons of ordinal and nonnormally distributed interval data the Wilcoxon signed rank test was used. Binary variables were compared using the Fisher exact test. For analysis of repeated measures of laboratory data, linear mixed-effects models were used with group allocation as fixed effect and participants clustered within centers as a random effect to account for within-participant and within-center correlation. Where appropriate, the model included the random slope term to reflect differing responses to the main factor of interest. Post hoc pairwise comparisons were adjusted for multiplicity using the Tukey single-step method. For computational purposes, modeling of laboratory data was performed on log-transformed values. Missing data were not imputed. Observations with no nonmissing values beyond baseline were excluded from analysis. Whenever possible, the last available value was included into mixed-effects analysis.

Sensitivity Analyses
To assess robustness of the treatment effect, we carried out a post hoc sensitivity analysis after excluding prolonged ventilation. Timing of extubation is prone to subjective judgement and thus may introduce bias when used as an end point. To remove this potential bias, in the sensitivity analysis patients who experienced only prolonged ventilation were counted as not having experienced the primary end point.
event. To account for the site effect, post hoc mixed-effects Cox regression modeling with the center as the random effect was used to estimate the treatment effect.

Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Statistical significance was set at the 2-sided .05 level. All analyses were performed using version 3.5.0 of R software (R Core Team, 2018; R: A language and environment for statistical computing; packages “survival,” “coxme,” “lme4,” “rms”).

Results

Between December 2015 and October 2018, 394 infants from 4 sites in Brazil, China, and Russia (accounting for 95% of recruitment) were randomized to receive dexamethasone (n = 194) or placebo (n = 200) (Figure 1). All 394 patients had primary end point follow-up data collected and were included in the analysis by randomization group. Information was not available regarding use of pacemakers for 2 patients (0.5%), serum creatinine measures for 2 patients (0.5%), and blood glucose levels for 7 patients (1.8%).

The 2 groups were well matched by baseline variables (Table I). The median age was 6 months, and 19 infants (4.8%) were younger than 30 days. For 10 patients, the surgical strategy changed after randomization, resulting in off-pump surgery (Figure I). For the remainder, the median duration of cardiopulmonary bypass was 50 minutes for patients in the dexamethasone group and 46 minutes for patient in the placebo group (eTable 5 in Supplement 2). Median rectal temperature was 36°C in both groups.

Overall, the composite primary end point event occurred among 74 patients (38.1%) in the dexamethasone group and 91 patients (45.5%) in the control group (absolute risk reduction, 7.4%; 95% CI, −0.8% to 15.3%; HR, 0.82; 95% CI, 0.60 to 1.10; P = .20) (Table 2).

Similarly to the primary analysis, individual components of the primary end point were not significantly different between groups. Overall, 2 patients (1.0%) in the dexamethasone group and 4 patients (2.0%) in the control group died during the study period. Acute kidney injury occurred in 10 patients (5.1%) in the dexamethasone group and 14 (7.0%) in the placebo group (P = .43). Prolonged ventilation (ie, ≥24 hours) occurred in 70 patients (36.1%) in the dexamethasone group and in 84 (42.0%) in the control group (P = .25). Six patients (3.1%) in the dexamethasone group and 13 (6.5%) in the placebo group experienced neurologic events.

Randomization code break occurred, and open-label steroids were administered to 30 patients (15.4%) in the dexamethasone group and 44 (22.0%) in the placebo group (P = .12), mostly due to suspected allergy (eTable 8 in Supplement 2).

The baseline serum glucose was a mean of 104 mg/dL (95% CI, 101 to 107 mg/dL) in the dexamethasone group vs 101 mg/dL (95% CI, 98 to 104 mg/dL) in control group, for a between-group difference of 3 mg/dL (95% CI, −2 to 7 mg/dL). At 24 hours postoperatively, the mean glucose level was 189 mg/dL (95% CI, 180 to 198 mg/dL) in the dexamethasone group and 168 mg/dL (95% CI, 161 to 175 mg/dL) in the control group, with a between-group mean difference of 21 mg/dL.
(95% CI, 9 to 32 mg/dL; P < .001). No statistically significant difference between groups in other laboratory data were recorded with details available in Supplement 2.

There were 4 cases (2.0%) of confirmed infection in the dexamethasone group and 3 (1.5%) in the control group. In the dexamethasone group, 3 patients had pneumonia and 1 patient had mediastinitis. In the control group, 2 patients developed pneumonia (accompanied by wound infection in 1 case) and 1 patient had deep sternal infection (for details, see eTable 6 in Supplement 2). No cases of sepsis were observed.

Subgroup analyses did not identify any statistically significant treatment effect across prespecified patient subgroups (Figure 2).

No statistically significant difference between groups in the primary end point in this post hoc analysis was observed after removing the most frequent component of the composite primary end point (prolonged mechanical ventilation) (HR, 0.66; 95% CI, 0.37-1.18; P = .16).

Adjustment for site did not significantly change the estimated treatment effect (HR, 0.80; 95% CI, 0.59-1.09; P = .15).

Discussion

In this clinical trial involving infants younger than 12 months who had congenital heart defects and were undergoing cardiac surgery with cardiopulmonary bypass, administration of 1 mg/kg of dexamethasone, compared with placebo, did not significantly reduce a composite outcome of major complications and mortality. Additionally, none of prespecified secondary end points differed significantly between groups. The trial was planned to detect a 15% difference in the primary composite end point, assuming a 40% incidence in the control group. Although the event rate in the control group was close to expected (ie, 45.5%) and similar to that observed in a recent study, there was no significant between-group difference in the composite end point.

Systemic inflammatory response plays a pivotal role in the development of complications after cardiac surgery. Increased levels of proinflammatory cytokines, complement and activation of endothelial cells leads to development of capillary leak syndrome, thereby deteriorating organ function.

The rationale of corticosteroids administration in patients with congenital heart diseases who undergo cardiac surgery is supported by several studies that showed attenuation of systemic inflammatory response after cardiopulmonary bypass. Reduction in proinflammatory cytokines levels was accompanied by better myocardial protection, less inotropes and fluid requirements, and better preservation of lung function after surgery. A double-blind study, Heying et al randomized 20 neonates to receive either 1 mg/kg of dexamethasone or placebo 4 hours before cardiopulmonary bypass. Pretreatment with dexamethasone was associated with significant reduction of troponin T concentration and lower dobutamine requirements. Adding 30 mg/kg methylprednisolone to the cardiopulmonary bypass prime solution before myocardial ischemia conferred cardiac protection in infants and young children. Nevertheless, clinical efficacy of corticosteroids in this setting remains controversial.

Recently, Graham et al in a double-blind study randomized 190 neonates in 2 centers to receive either 30 mg/kg of methylprednisolone or placebo after anesthesia induction. The morbidity-mortality composite primary end point occurred in 27 (33%) patients in the methylprednisolone group and in 40 (42%) in the placebo group (odds ratio, 0.63; 95% CI, 0.31 to 1.3), suggesting lack of benefit associated with the use of methylprednisolone in this cohort of patients undergoing cardiac surgery with cardiopulmonary bypass. Although the study by Graham et al included only neonates, the current study randomized patients younger than 12-month, an age group that comprises the majority of...
patients with congenital heart defects undergoing cardiac surgery worldwide.

The current study failed to confirm that administration of corticosteroids was associated with lower risk of acute kidney injury observed in the meta-analysis of Scrascia et al.30 In this meta-analysis, only 2 studies with no strict definitions of acute kidney injury and a small number of patients (49 patients in total) addressed the association of corticosteroids on

Table 2. Primary End Point Analysis

<table>
<thead>
<tr>
<th>Events, No. (%)</th>
<th>Kaplan-Meier 30-d event rate, %</th>
<th>Absolute reduction (95% CI)*</th>
<th>HR (95% CI)*</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone (n = 194)</td>
<td>Placebo (n = 200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point (death, nonfatal myocardial infarction, need for ECMO, CPR, AKI, ventilation ≥24 h, or neurologic event)</td>
<td>74 (38.1)</td>
<td>91 (45.5)</td>
<td>38.1</td>
<td>45.5</td>
</tr>
<tr>
<td>Components of primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation ≥24 h</td>
<td>70 (36.1)</td>
<td>84 (42.0)</td>
<td>36.1</td>
<td>42.0</td>
</tr>
<tr>
<td>AKI</td>
<td>10 (5.2)</td>
<td>14 (7.0)</td>
<td>5.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Neurologic event (stroke, or seizures, or coma)</td>
<td>6 (3.1)</td>
<td>13 (6.5)</td>
<td>3.2</td>
<td>6.6</td>
</tr>
<tr>
<td>CPR</td>
<td>4 (2.1)</td>
<td>5 (2.5)</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.0)</td>
<td>4 (2.0)</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>ECMO</td>
<td>1 (0.5)</td>
<td>3 (1.5)</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>2 (1.0)</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury (at least stage “Injury” according to the Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease scale: estimated creatinine clearance decrease by 50%, urine output <0.5 mL/kg/h for 16 h)16; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio.

a For comparing dexamethasone group vs control group.

P value from a univariable Cox regression model (ie, Wald test) with a time-to-event object as the dependent variable and group as the explanatory variable.

b Patients who experienced more than 1 of the component events are counted only once for the primary end point comparison based on the time to first event. The individual components may not sum to the number of patients with a primary end point event.

Figure 2. Primary End Point Subgroup Analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of events/patients (person-days)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td>Dexamethasone</td>
<td>Placebo</td>
</tr>
<tr>
<td>Boys</td>
<td>40/93 (1566)</td>
<td>47/93 (1332)</td>
<td>0.81 (0.53-1.24)</td>
</tr>
<tr>
<td>Girls</td>
<td>34/101 (1983)</td>
<td>44/107 (1870)</td>
<td>0.77 (0.49-1.20)</td>
</tr>
<tr>
<td>Age, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>11/11 (11)</td>
<td>8/8 (8)</td>
<td>0.88 (0.35-2.19)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>63/183 (3539)</td>
<td>63/192 (3195)</td>
<td>0.75 (0.54-1.05)</td>
</tr>
<tr>
<td>Cyanotic defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32/58 (690)</td>
<td>36/55 (573)</td>
<td>0.86 (0.53-1.41)</td>
</tr>
<tr>
<td>No</td>
<td>42/136 (2859)</td>
<td>55/145 (2599)</td>
<td>0.75 (0.50-1.12)</td>
</tr>
<tr>
<td>Circulatory arresta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8/8 (8)</td>
<td>3/3 (3)</td>
<td>1.52 (0.39-5.86)</td>
</tr>
<tr>
<td>No</td>
<td>66/186 (3451)</td>
<td>88/197 (3020)</td>
<td>0.75 (0.54-1.03)</td>
</tr>
<tr>
<td>Surgery on fibrillating heartb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1/36 (1021)</td>
<td>6/34 (755)</td>
<td>0.15 (0.02-1.22)</td>
</tr>
<tr>
<td>No</td>
<td>73/158 (2438)</td>
<td>85/166 (2267)</td>
<td>0.83 (0.61-1.14)</td>
</tr>
<tr>
<td>Post hoc analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novosibirsk, Russia</td>
<td></td>
<td>56/159 (3099)</td>
<td>60/160 (2732)</td>
</tr>
<tr>
<td>Penza, Russia</td>
<td>13/27 (410)</td>
<td>17/29 (343)</td>
<td>0.74 (0.36-1.53)</td>
</tr>
<tr>
<td>Sao Paulo, Brazil</td>
<td></td>
<td>4/5 (38)</td>
<td>4/8 (127)</td>
</tr>
<tr>
<td>Shanghai, China</td>
<td></td>
<td>1/3 (62)</td>
<td>1/3 (62)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>74/194 (3609)</td>
<td>91/200 (3264)</td>
</tr>
</tbody>
</table>

The squares indicate the hazard ratios, the error bars, 95% CIs; the dotted line, no treatment effect; the dashed line, the observed overall treatment effect.

a Temporary interruption of circulation during the complex cardiovascular repair.

b Surgery with induced heart fibrillation without aortic cross-clamping.
worsening of renal function. On the contrary, the current study which had a large number of patients, a uniform definition of acute kidney injury, and a rigorous trial methodology failed to confirm the renoprotective properties of dexamethasone. Safety of corticosteroids in the pediatric population undergoing cardiac surgery is questioned. Retrospective analysis of the Society of Thoracic Surgeons Database from 25 participating centers including 3180 neonates showed an increased incidence of postoperative infectious complications after methylprednisolone administration, especially in low-risk patients.2,3 This could be explained by glucocorticoid-induced hepatic gluconeogenesis with impaired glucose utilization leading to hyperglycemia that negatively affects immunity.3,4 Inhibition of wound healing induced by glucocorticoids may also contribute to development of infectious complications. Although in this study dexamethasone use was associated with significantly increased serum glucose at 24 hours postoperatively, dexamethasone use did not result in an increased risk of infection. Low-event rates of infectious complications (4 patients [2.0%] in dexamethasone group and 3 [1.5%] in the control group) precluded definitive conclusions, however.

Two large multicenter randomized clinical trials involving adult patients undergoing cardiac surgery did not demonstrate reduced major complications attributable to glucocorticoid use.5-10 Moreover, there was a risk of myocardial injury when even low doses (500 mg) of methylprednisolone was administered.10 Guidelines for adult cardiac surgery do not recommend the routine use of dexamethasone prophylactically in an effort to reduce complications.32 The findings of the current study suggests that the same recommendation may apply for pediatric cardiac surgery. Although no guidelines regarding the management of pediatric patients undergoing cardiac surgery under cardiopulmonary bypass exist, this question should be addressed in future recommendations. In this context, results of the ongoing large multicenter Steroids to Reduce Systemic Inflammation After Infant Heart Surgery (STRESS) trial of methylprednisolone administration among neonates undergoing cardiac surgery (ClinicalTrials.gov Identifier: NCT03229538) are awaited with interest.

There are several strengths of this study. To our knowledge, this trial is the largest randomized clinical trial ever performed in this field. The primary end point event rate in the control group matched the expectation used for power estimation. In addition, a relatively high dose of dexamethasone was used in the trial (ie, 1 mg/kg) in an attempt to obtain clinically significant effects.

Limitations
This study has several limitations. First, the trial might have overestimated the treatment effect and might be underpowered because the 95% CIs for the between-group difference in the primary end point included the minimally clinically important difference of 15%. Second, because proinflammatory and anti-inflammatory cytokines were not measured, it is unclear whether the dose of 1 mg/kg of dexamethasone was effective in reducing systemic inflammatory reaction. Nevertheless, the dose was sufficient to induce laboratory differences between groups (ie, hyperglycemia). Third, multicentric and multinational setting may be a limitation of the study because no strict protocol of anesthetic management was used.

Fourth, 71 patients received open-labeled dexamethasone postoperatively. Nevertheless, the numbers of these patients were similar between the 2 groups. Fifth, the higher level of glucose in the dexamethasone group on postoperative day 1 might have potentially resulted in unblinding of patient's allocation. Sixth, the composite end point used in this study has not been validated previously. Seventh, the small numbers in some patient subgroups (eg, neonates) resulted in imprecision of treatment effect estimates in subpopulations.

Conclusions
Among infants younger than 12 months undergoing cardiac surgery with cardiopulmonary bypass, intraoperative administration of dexamethasone, compared with placebo, did not significantly reduce major complications and mortality at 30 days. However, the study may have been underpowered to detect a clinically important difference.
independent data and safety monitoring board to monitor safety and had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

REFERENCES


