Stress-Dose Corticosteroid Versus Placebo in Neonatal Cardiac Operations: A Randomized Controlled Trial

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Background. **Corticosteroids can improve the hemodynamic status of neonates with postoperative low cardiac output syndrome after cardiac operations. This study compared a prophylactically administered stress-dose corticosteroid (SDC) regimen against placebo on inflammation, adrenocortical function, and hemodynamic outcome.**

Methods. **Forty neonates undergoing elective open heart operations were randomized into two groups. The SDC group received perioperatively 2 mg/kg methylprednisolone, and 6 hours after the operation, a hydrocortisone infusion (0.2 mg/kg/h) was started with tapering doses for 5 days. Placebo was administered in a similar fashion. An adrenocorticotropic hormone stimulation test was performed after the therapy. The primary endpoint of the study was plasma concentration of interleukin (IL-6). Secondary clinical outcomes included plasma cortisol, IL-10, C-reactive protein, echocardiographic systemic ventricle contractility evaluated by the Velocity Vector Imaging program, the inotropic score, and time of delayed sternal closure.**

Results. **The IL-6 values of the SDC group were significantly lower postoperatively than in the placebo group. Significantly lower inotropic scores ($p < 0.05$), earlier sternal closure ($p = 0.03$), and less deterioration in the systemic ventricle mean delta strain values between the preoperative and the first postoperative assessment ($p = 0.01$) were detected for the SDC group. The SDC therapy did not suppress the hypothalamic-pituitary-adrenal axis more than placebo. The mean plasma cortisol level did not decline in the placebo group after the operation.**

Conclusions. **The SDC regimen for 5 days postoperatively in neonates was safe and did not cause suppression of the hypothalamic-pituitary-adrenal axis. Furthermore, the open heart operation per se did not lead to adrenal insufficiency in neonates.**

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The timing, optimal dosing, and the length of steroid administration have not been standardized in children undergoing cardiac operations, which may partly explain the variation in the benefits of steroids in addition to their known antiinflammatory effects [1–6]. Corticosteroid treatment has been reported to improve hemodynamics in infants with low cardiac output syndrome after cardiac operations [7]. Placebo-controlled observations on the potential benefits of prophylactic postoperative "stress dosing" by hydrocortisone infusion in neonates undergoing cardiac operations include a reduction of the inflammatory response and the lower incidence of low cardiac output syndrome, improved fluid balance, and prevention of adrenal insufficiency (AI) [8, 9]. However, knowledge is lacking about the appropriate plasma cortisol level after cardiac operations and its effect on the postoperative outcome [10–14].

The present randomized, double-blinded, placebo-controlled study was designed to compare the antiinflammatory response (primary end point), adrenocortical function, and hemodynamic outcome of stress-dose corticosteroid (SDC) and placebo groups. Our hypothesis was that neonates receiving a bolus of 2 mg/kg methylprednisolone in the operating room, followed by hydrocortisone infusion in the pediatric intensive care unit (PICU), should have a decreased inflammatory response and better cardiac contractility compared with the placebo group. Furthermore, we wanted to assess the safety of SDC treatment.

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Patients and Methods

Ethics and Informed Consent

The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital (January 31, 2012) and by the Finnish Medicines Agency (January 9, 2012). The study was also registered in the European Union Clinical Trials Register (Eudra-CT 2011-005239-14). Written informed consent was obtained from all parents of the patients before the study commenced.

Study Design

Forty neonates (age ≤28 days) who were undergoing nonemergency cardiac operations with cardiopulmonary bypass (CPB) between April 2012 and October 2014 were randomized by sealed envelope into two groups. Exclusion criteria were symptoms related to prematurity or birth before 36 weeks of gestational age, chromosomal abnormalities, administration of corticosteroids before the operation, and the need of preoperative inotropic support other than milrinone.

After the induction of anesthesia, the control group received placebo and the intervention group received an intravenous bolus of 2 mg/kg methylprednisolone, the smallest dose shown to be effective in children undergoing cardiac operations [15]. A hydrocortisone infusion in the intervention group was started 6 hours after the weaning from the CPB at the rate of 0.2 mg/kg/h for 48 hours, 0.1 mg/kg/h for 48 hours, and 0.05 mg/kg/h for 24 hours. The initial hydrocortisone infusion dose was based on the recommendation for glucocorticoid replacement therapy for critically ill patients [16]. The study drug was discontinued if the patient was discharged from the PICU earlier than postoperative day (POD) 5. A placebo saline infusion was administered to the control group in a similar tapering dosing regimen.

A pharmacist who was not involved in the care of the patients prepared methylprednisolone, hydrocortisone, and placebo solutions with 0.9% saline. All study and clinical personnel were blinded to the treatment allocation until the study period ended. No additional steroids were administered during the study period. The study drug infusion was allowed to stop at the discretion of the PICU physician, if the patient was in low cardiac output and was assumed to benefit from the administration of hydrocortisone.

End Points and Definition

The primary end point of the study was plasma concentration of interleukin (IL-6). Secondary clinical outcomes included plasma cortisol, echocardiographic systemic ventricle contractility evaluated by the Velocity Vector Imaging (VVI) program (syngo USWP 3.0; Siemens Medical Solutions, Erlangen, Germany), and the inotrope score; biochemical variables (lactate, central venous saturation), inflammation markers (IL-10, C-reactive protein), and clinical outcome variables such as length of mechanical ventilation and PICU stay, time of delayed sternal closure, and ventilator-free days at 28 days after PICU admission. Patients who did not survive to day 28 were assigned zero ventilator-free days. Fluid balance and the vasoactive inotropic score were calculated at 1200 hours on the postoperative day. Elevated blood glucose (>10 mmol/L) and nosocomial infections (data retrieved from the infection registry of the Children's Hospital) were reported as adverse events potentially related to the use of corticosteroids.

Intraoperative Management

Balanced general anesthesia was attained by sufentanil, pancuronium, S-ketamine, and sevoflurane. CPB management and myocardial protection were accomplished with the same methods described in our previous article [17]. Three surgeons operated on all the study patients. The patient's chest was left open at the surgeon's discretion to prevent cardiac compression and hemodynamic instability. The threshold was kept quite low to avoid the possible emergency reopening of the chest during the immediate postoperative period.

Inotrope and Insulin therapy

Milrinone and levosimendan were used as the first-line inotropes at the discretion of the anesthesiologist in charge of the patient. Epinephrine and norepinephrine were added for hemodynamic support when needed. The inotropic score for vasoactive drugs was calculated as described earlier [17]. Inhaled nitric oxide was used after weaning from CBP in neonates with pulmonary hypertension. Insulin was administered in the PICU if blood glucose concentrations were greater than 10 mmol/L in two repeated measurements.

Blood Samples

Blood samples were collected into tubes containing sodium citrate at eight different times: at anesthesia induction before the bolus methylprednisolone or placebo was administered (T1), 5 minutes after weaning from CPB (T2), 6 hours after weaning from CPB before hydrocortisone or placebo infusion, and at 6 A.M. (T3), and for 5 postoperative days thereafter (T4–8). Plasma was immediately separated by centrifugation and stored at –70°C until analysis. IL-6 and IL-10 concentrations were determined at T1 to T6 inclusive using enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems, Abington, United Kingdom). Total plasma concentration of methylprednisolone was determined using a high-performance liquid chromatography-electrospray-tandem mass spectrometry method, as described earlier [3].

The adrenocorticotropic hormone (ACTH) stimulation test was performed on the following morning at 6 A.M. after the study drug infusion had discontinued. Adrenal function and hypothalamic-pituitary-adrenal integrity were assessed by ACTH adrenal stimulation with 250 μg/1.73 m^2 or 1 μg/1.73 m^2 intravenous cosyntropin (Cortrosyn; Amphastar, Rancho Cucamonga, CA). Serum cortisol levels were measured at baseline and 30 minutes after stimulation. AI was defined as a baseline cortisol level 5 μg/dL or an increase of less than 16 μg/dL in the post-ACTH simulation level [18].