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Preoperative steroid treatment does not improve markers of inflammation after cardiac surgery in neonates: Results from a randomized trial

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Objective: Neonatal cardiac surgery requiring cardiopulmonary bypass results in a heightened inflammatory response. Perioperative glucocorticoid administration is commonly used in an attempt to reduce the inflammatory cascade, although characterization of the cytokine response to steroids in neonatal cardiac surgery remains elusive because of highly variable approaches in administration. This randomized trial was designed to prospectively evaluate the effect of specific glucocorticoid dosing protocols on inflammatory markers in neonatal cardiac surgery requiring cardiopulmonary bypass.

Methods: Neonates scheduled for cardiac surgery were randomly assigned to receive either 2-dose (8 hours preoperatively and operatively, n = 36) or single-dose (operatively, n = 32) methylprednisolone at 30 mg/kg per dose in a prospective double-blind trial. The primary outcome was the effect of these steroid regimens on markers of inflammation. Secondary analyses evaluated the association of specific cytokine profiles with postoperative clinical outcomes.

Results: Patient demographics, perioperative variables, and preoperative indices of inflammation were similar between the single- and 2-dose groups. Preoperative cytokine response after the 2-dose methylprednisolone protocol was consistent with an anti-inflammatory effect, although this did not persist into the postoperative period. Premedication baseline levels of interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor α were predictive of postoperative intensive care unit and hospital length of stay. Only interleukin-8 demonstrated a postoperative response associated with duration of intensive care unit and hospital stay.

Conclusions: The addition of a preoperative dose of methylprednisolone to a standard intraoperative methylprednisolone dose does not improve markers of inflammation after neonatal cardiac surgery. The routine administration of preoperative glucocorticoids in neonatal cardiac surgery should be reconsidered. (J Thorac Cardiovasc Surg 2014;147:902-8)

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Cardiopulmonary bypass (CPB) is a complex pathophysiologic environment in which exposure to nonphysiologic surfaces in the pump circuit, hemolysis, and ischemia-reperfusion injury combine to initiate a complex cascade that includes proinflammatory cytokines, anti-inflammatory cytokines, and products of neutrophil activation.[1-3] The inflammatory consequences from CPB culminate in a systemic inflammatory response syndrome. The systemic inflammatory response syndrome is further exacerbated in neonates because of morbidity factors of smaller patient size, greater hemodilution, hypothermia, and longer CPB times, resulting in a postoperative recovery period that is longer and more complex than similar operations performed in older infants and children.[4-6]

Clinical appreciation of this post-CPB inflammatory response has resulted in several interventions directed toward its reduction.[7-9] Glucocorticoid administration is among the most common method to attenuate the clinical and biochemical features of the post-CPB inflammatory response, although the technique of steroid administration in neonatal cardiac surgery is highly variable.[8,9] To further

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
ICU = intensive care unit
IL = interleukin
LCOS = low cardiac output syndrome
MP = methylprednisolone
TNF = tumor necrosis factor

confound matters, the few studies investigating clinical outcomes associated with the use of corticosteroids in children requiring CPB yield contradictory results.[10-13]

Given the intertwined and redundant inflammatory cascade and the highly variable clinical practices in neonatal preoperative and intraoperative care, characterizing the anti-inflammatory response of steroids in neonatal cardiac surgery has remained elusive. Accordingly, this randomized trial was designed to prospectively evaluate the effect of uniform and specific glucocorticoid dosing protocols on inflammatory markers in the context of neonatal cardiac surgery requiring CPB.

METHODS

Patient Selection, Enrollment, and Randomization

The study was approved by the Institutional Review Board, and informed written consent was obtained from the parent or legal guardian in accordance with all policies and regulations regarding obtaining informed consent of a minor. The study was part of a clinical outcomes trial, and the design details and clinical outcomes have been published (ClinicalTrials.gov Identifier: NCT00934843).[10] In brief, inclusion criteria consisted of all inpatient neonates (aged $\leq$30 days) scheduled to undergo a cardiac operation requiring CPB. Exclusion criteria included prematurity (defined as $\leq$36 weeks' postmenstrual age) at the time of surgery, treatment with steroids in the 2 weeks before surgery, suspected infection that would contraindicate steroid use (eg, herpes), known hypersensitivity to methylprednisolone (MP), or other contraindication to steroid therapy (eg, gastrointestinal tract bleeding). Subjects were randomly assigned to either preoperative placebo (approximately 8 hours preoperatively) and intraoperative MP at 30 mg/kg of body weight (single-dose group) or preoperative and intraoperative MP (2-dose group) within strata, according to planned corrective or palliative operation. All investigation and clinical site personnel were blinded to the treatment allocation until the close of the study.

Outcome Variables

The primary outcome was markers of inflammation after administration of specific glucocorticoid dosing protocols. The correspondence of cytokine profiles with clinical outcomes, such as low cardiac output syndrome (LCOS) and intensive care unit (ICU) and hospital stays, was investigated in secondary analyses. The presence of LCOS was defined by the clinicial signs and symptoms of low cardiac output (eg, tachycardia, oliguria, cold extremities, and cardiac arrest) that require 1 or more of the following interventions: mechanical circulatory support, the escalation of exisiting pharmacologic circulatory support to more than 100% over baseline, or the inititation of new pharmacologic circulatory support.[14] The determination of LCOS was made by 2 independent reviewers (E.M.G., A.M.A.) and then agreed on between both reviewers before unblinding. Markers of inflammation were compared between treatment groups, which included the plasma levels of the proinflammatory cytokines, interleukin (IL)-2, IL-6, IL-8, tumor necrosis factor α (TNF-α), and interferon-γ, and the anti-inflammatory cytokine, IL-10. The rationale for the selection of these cytokines was to survey both proinflammatory and anti-inflammatory markers. Samples were collected at 6 time points: (1) "baseline," before preoperative placebo/MP treatment (approximately 8 hours preoperatively), (2) immediately before skin incision, (3) on completion of modified ultrafiltration, and at (4) 4 hours, (5) 12 hours, and (6) 24 hours postoperatively. Whole blood samples of 1 mL were collected in ethylenediaminetetraacetic acid tubes at each of the 6 time points. Plasma was isolated by centrifugation, decanted into aliquots, and stored at -80°C until processed for immunoassays.

Plasma levels of cytokines were determined by multiplex suspension array using commercially available and validated kits (R&D Systems, Minneapolis, Minn).[3] Plasma values were corrected for hemodilution using hematocrit values. All samples were batched and run simultaenously to avoid potential laboratory assay variance. Patients enrolled in the parent study were included in this analysis if they had an adequate volume of plasma at each of the 6 time points to analyze all inflammatory markers. Plasma-free hemoglobin, as a measurement of hemolysis, was obtained postoperatively on arrival to the ICU.

Statistical Analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data. Continuous demographic characteristics are listed as means and associated SDs and were compared between groups using a *t*-test. Categorical characteristics are expressed as the number and percentage of subjects and were compared using a normal Pearson χ^2 test statistic. Because of their skewed distributions, baseline measures of inflammatory markers are expressed as the median and interquartile range and are compared across steroid groups using a Wilcoxon rank-sum test statistic. Preoperative indices of inflammation were measured at "baseline" before administration of the preoperative steroids (or placebo) and again before surgery (preincision). To appraise the pharmacologic effect of preoperative MP steroid dose on cytokine levels, an analysis of variance model was used, fitting the preoperative steroid levels while controlling for the baseline premedication levels.

To assess the effect of steroid treatment on the cytokine profiles after surgery, a linear mixed-effect model was used. Restricted maximum likelihood methods were used to estimate the fixed effects and variance components in the presence of unbalanced data.[15] Baseline cytokine values (premed), randomized treatment assignment, and aprotinin use status were used as covariates in a regression model, and estimate statements were used to construct group-level mean tests across steroid treatment groups at each time point. All cytokine post hoc pairwise comparison results are adjusted using the Bonferonni method. Because of the highly skewed and nonnormal distributions of the markers of inflammation, the values were $\log_{10}$ transformed before model analysis.

To test whether baseline or peak cytokine levels are associated with clinical postoperative outcomes (ICU and hospital lengths of stay), regression models were developed that adjusted for study design variables (randomized steroid treatment group and aprotinin administration). Independent associations were present between sex and surgery type (corrective vs palliative) with both ICU and hospital lengths of stay. Thus, all regression models were additionally adjusted for both characteristics. To test whether increases in baseline or peak cytokine levels are associated with higher odds to develop postoperative LCOS, similarly adjusted logistic regression models were developed. Statistical analyses were performed with SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Preoperative Demographics and Intraoperative Variables

Enrollment and outcomes have been previously reported.[10] Briefly, 97 patients were screened for enrollment, and 78 met all inclusion/exclusion criteria and were randomized.