A composite outcome for neonatal cardiac surgery research

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Objective: The objective of this study was to determine whether a composite outcome, derived of objective signs of inadequate cardiac output, would be associated with other important measures of outcomes and therefore be an appropriate end point for clinical trials in neonatal cardiac surgery.

Methods: Neonates (n = 76) undergoing cardiac operations requiring cardiopulmonary bypass were prospectively enrolled. Patients were defined to have met the composite outcome if they had any of the following events before hospital discharge: death, the use of mechanical circulatory support, cardiac arrest requiring chest compressions, hepatic injury (2 times the upper limit of normal for aspartate aminotransferase or alanine aminotransferase), renal injury (creatinine >1.5 mg/dL), or lactic acidosis (an increasing lactate >5 mmol/L in the postoperative period). Associations between the composite outcome and the duration of mechanical ventilation, intensive care unit stay, hospital stay, and total hospital charges were determined.

Results: The median age at the time of surgery was 7 days, and the median weight was 3.2 kg. The composite outcome was met in 39% of patients (30/76). Patients who met the composite outcome compared with those who did not had a longer duration of mechanical ventilation (4.9 vs 2.9 days, $P < .01$), intensive care unit stay (8.8 vs 5.7 days, $P < .01$), hospital stay (23 vs 12 days, $P < .01$), and increased hospital charges ($258,000 vs $170,000, $P < .01$). In linear regression analysis, controlling for surgical complexity, these differences remained significant ($R^2 = 0.29$-0.42, $P < .01$).

Conclusions: The composite outcome is highly associated with important early operative outcomes and may serve as a useful end point for future clinical research in neonates undergoing cardiac operations. (J Thorac Cardiovasc Surg 2014;147:428-33)

CHD

Advancements in surgical techniques and refinements in perioperative management have led to significant improvements in survival after neonatal cardiac surgery, yet significant morbidity persists.[1-3] Accordingly, research has shifted from not only improving survival but also reducing morbidity.[4] However, research in pediatric heart disease is confronted by barriers, including small numbers of subjects with a particular congenital heart defect at any one center, differences in treatment approaches resulting in a lack of therapeutic equipoise, and lack of validated outcome measures. Multi-institutional collaboration, such as the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network, and registries have been developed to improve sample size and facilitate scientific investigation.[5] However, validation of outcomes remains relatively unexplored. In congenital cardiac surgery, commonly used outcomes include mortality, duration of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay.[6,7] In the neonatal population, these outcomes often can be problematic because mortality is infrequent, and the other outcomes often have a wide range or large standard deviation resulting in inadequately powered studies or the need for a large sample size. Many investigators have used surrogate outcome measures, such as low cardiac output syndrome, inotropic score, and vasoactive inotropic score.[6-8] Despite the intuitive nature of these outcomes, a recent report demonstrated that low cardiac output syndrome had a poor association and vasoactive inotropic score had weak correlations with other clinically important outcomes in neonates undergoing cardiac operations.[9] This highlights the need for further investigation into the validation of superior surrogate outcome measures in neonatal cardiac surgery.

An ideal early outcome measure would be easily measured, reproducible, and, most important, independently correlated with other measures of short- and long-term outcomes. Composite outcomes, which combine several components into a single measure, have gained popularity in the

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This study was supported in part by a Career Development Award from the American College of Cardiology Foundation/Pfizer Scholarship (to Dr Graham) and by Award Number UL1RR029882 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 15, 2012; revisions received Jan 17, 2013; accepted for publication March 8, 2013; available ahead of print April 15, 2013.

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0022-5223/$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

http://dx.doi.org/10.1016/j.jtcvs.2013.03.013

Abbreviations and Acronyms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CI = confidence interval
CPB = cardiopulmonary bypass
CPR = cardiopulmonary resuscitation
ECMO = extracorporeal membrane oxygenation
ICU = intensive care unit
IQR = interquartile range
RACHS-1 = Risk Adjustment for Congenital Heart Surgery 1

scientific community.[10] The advantages supporting the use of a composite outcome are that it increases statistical efficiency because of higher event rates, which reduces sample size requirement, cost, and time, and that it allows investigators to avoid an arbitrary choice between several important outcomes.[11] These advantages have resulted in the widespread use of composite outcomes in clinical trials, including pediatric heart disease.[12-14] The objective of this study was to use a standardized composite outcome for neonatal cardiac surgery in a well-characterized cohort and correlate this composite outcome with other important early postoperative outcomes.

MATERIALS AND METHODS

The study is a secondary analysis of a prospective randomized controlled trial comparing preoperative glucocorticoid therapy in 76 neonates (ClinicalTrials.gov Identifier NCT00934843).[15] The study was approved by the Medical University of South Carolina's Institutional Review Board, and informed written consent was obtained from the parent or legal guardian of all participants.

Composite Outcome

The individual components of the composite outcome were composed of clinical and laboratory signs of inadequate tissue oxygen delivery or circulatory collapse. Six components were chosen because each represents important early clinical outcomes, often resulting from low cardiac output, and have been associated with poor outcomes in other studies.[16-21] The components include death, circulatory collapse requiring chest compressions (cardiopulmonary resuscitation [CPR]), mechanical circulatory support (extracorporeal membrane oxygenation [ECMO]), hepatic insufficiency, renal insufficiency, and lactic acidosis. Hepatic injury was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2 times the upper limit of normal (normal range, AST 8-40 IU/L; hepatic injury, AST >80 IU/L; normal range, ALT 7-40 IU/L; hepatic injury, ALT >80 IU/L). Elevated AST within the first 24 postoperative hours was not considered hepatic insufficiency because AST elevation was likely a result of hemolysis related to cardiopulmonary bypass (CPB).[22] Renal injury was defined by an increase in creatinine during admission greater than 2 times the upper limit of normal (normal range, 0.3-0.7; renal injury, >1.5 mg/dL). Lactic acidosis was defined as an increasing arterial lactate concentration that reached more than 5 mmol/dL postoperatively.[16,23] Patients who experienced any of the 6 components after cardiac surgery and before hospital discharge were considered to have met the composite outcome.

Liver function panels were ordered as part of the study protocol on arrival to the ICU and 36 hours after arrival. Additional liver function tests were obtained as clinically indicated and analyzed for the composite outcome. Serum creatinine was measured on arrival to the ICU from the operating room and then daily for a minimum of 2 days. It was common practice during the study period to have creatinine levels checked daily while in the ICU if arterial or central venous access was present; however, this practice was not required by the study protocol. Lactate levels were obtained via arterial catheters and obtained on arrival to the ICU and at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours postoperatively at a minimum and more often as clinically indicated.

Study Population

All inpatient neonates (aged ≤30 days) scheduled to undergo cardiac surgery involving CPB from July 2007 to July 2009 were eligible for this study. Exclusion criteria included prematurity (defined as ≤36 weeks gestational age at the time of surgery), previous treatment with or contraindication to steroid therapy, or preoperative use of mechanical circulatory support or active resuscitation at the time of proposed randomization. Patients were randomly assigned to preoperative placebo and intraoperative methylprednisolone (1 dose) or preoperative and intraoperative methylprednisolone (2 doses). Details on the study population have been reported.[15]

Data Analysis

The characteristics of the patients who met the composite outcome were compared with those who did not with respect to surgical complexity by the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) classification,[24] age at surgery, weight at surgery, length of CPB, use of aprotinin, or delayed sternal closure. Continuous data were compared using the Wilcoxon rank-sum test; categoric data were analyzed with the chi-square test. Patients who met the composite outcome were compared with those who did not with respect to duration of postoperative mechanical ventilation, ICU stay, hospital stay, and hospital charges using the Wilcoxon rank-sum test.

To explore the associations between meeting more than 1 criteria or meeting the more clinically significant criteria and outcomes, patients were further separated into 3 groups based on the number of composite outcome criteria met: none, only 1, and more than 1. Patients were further classified as meeting 1 of the clinical criteria (CPR, ECMO, death), laboratory criteria only (hepatic or renal injury, lactic acidosis), or no criteria. Comparisons were made between groups using the Kruskal–Wallis test for nonparametric data. Because patients who die in the hospital often have more extensive resource use, sensitivity analyses were performed to determine whether findings changed significantly when those patients (n = 2) were excluded.

To perform linear regression analysis, postoperative outcomes were log-transformed to create parametric distribution. Surgical complexity was controlled in the regressions analysis by dichotomizing patients with a RACHS-1 class of 5 or 6 and patients with a RACHS-1 class of 2 to 4. An alpha level less than 0.05 was considered statistically significant.

RESULTS

All 76 patients had complete records for review and were included in the analysis. Patient demographics, cardiac diagnoses, surgical procedures performed, and intraoperative parameters have been described.[15] Median gestational age was 39 weeks (interquartile range [IQR], 38-39.3). Median weight at surgery was 3.2 kg (IQR, 2.9-3.5). Diagnostic classification based on RACHS-1 class is shown in Table 1.

Of the 76 patients, 30 (39%) met the composite outcome. There were 2 deaths before hospital discharge, resulting in