Hypogammaglobulinemia after cardiopulmonary bypass in infants

Leslie A. Rhodes, MD,[a] Stephen M. Robert, MD,[a] T. Prescott Atkinson, MD,[b] Robert J. Dabal, MD,[c] Alla M. Mahdi, MPH,[d] and Jeffrey A. Alten, MD[a]

Background: Hypogammaglobulinemia has been reported after cardiac surgery and may be associated with adverse outcomes. We sought to define baseline immunoglobulin (Ig) concentration in neonates and infants with congenital heart disease, determine their course after cardiopulmonary bypass (CPB), and determine if post-CPB hypogammaglobulinemia was associated with increased morbidity.

Methods: This was a single-center, retrospective analysis of infants who underwent cardiac surgery with CPB between June 2010 and December 2011. The Ig concentration was obtained from banked plasma of 47 patients from a prior study (pre-CPB, immediately post-CPB, and 24 and 48 hours post-CPB). In addition, any Ig levels drawn for clinical purposes after CPB were included. Ig levels were excluded if drawn after chylothorax diagnosis or intravenous IgG administration.

Results: The median age was 7 days. Preoperative Ig concentration was similar to that described in healthy children. IgG level decreased to less than 50% of preoperative concentration by 24-hour post-CPB and failed to recover by 7 days. Of 47 patients, 25 (53%) had low IgG (<248 mg/dL) after CPB. Despite no difference in demographics or risk factors between patients with low and normal IgG, low IgG patients had more positive fluid balance at 24 hours and increased proinflammatory plasma cytokine levels, duration of mechanical ventilation, and cardiac intensive care unit length of stay. In addition, low IgG patients had an increased incidence of postoperative infections (40% vs 14%; $P = .056$).

Conclusions: Hypogammaglobulinemia occurs in half of infants after CPB. Its association with fluid overload and increased inflammatory cytokines suggests it may result from capillary leak. Postoperative hypogammaglobulinemia is associated with increased morbidity, including more secondary infections. (J Thorac Cardiovasc Surg 2014;147:1587-93)

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Supplemental material is available online.

Postoperative hypogammaglobulinemia has been described in children and adults undergoing cardiac surgery with cardiopulmonary bypass (CPB). Potential causes may include hemodilution, destruction of immunoglobulin (Ig) by CPB, and extravasation into the interstitial space due to systemic inflammation and capillary leak syndrome.[1-3] Losses due to proteinuria and sequestration into the peritoneal and pleural spaces may contribute as well.[4,5] IgG is an integral component of the humoral immune system, and hypogammaglobulinemia has been associated with infectious risk in other populations.[6,7] Pre- and 24-hour post-CPB Ig concentrations in older children have been described,[8] but the incidence and clinical importance of post-CPB hypogammaglobulinemia in neonates and infants undergoing cardiac surgery with CPB are unknown.

We designed this study with the following aims: (1) to determine the normal preoperative range of IgG, IgM, and IgA in neonates with congenital heart disease; (2) to determine the impact of CPB on postoperative Ig concentrations; and (3) to determine whether hypogammaglobulinemia is associated with increased postoperative morbidity, including nosocomial infection. We hypothesized that hypogammaglobulinemia is common in neonates and infants after CPB and is associated with increased morbidity.

METHODS

Patients and Data Collection

This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. This is a retrospective study evaluating preoperative and postoperative plasma Ig concentrations (IgA, IgG, and IgM) in children undergoing complex cardiac surgery with CPB from June 1, 2010, to December 31, 2011, at our institution. Because of its retrospective design, informed consent was not required. Ig concentrations were acquired for inclusion via 2 methods: (1) analysis of banked plasma obtained from 47 consecutively enrolled subjects for a prior study that evaluated the impact of early postoperative peritoneal dialysis (PD) on neonates

From the Section of Cardiac Critical Care[a] and the Division of Allergy,[b] Department of Pediatrics, the Division of Cardiothoracic Surgery,[c] Department of Surgery, and the School of Medicine,[d] University of Alabama at Birmingham, Birmingham, Ala.

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Address for reprints: Jeffrey A. Alten, MD, Department of Pediatrics, University of Alabama at Birmingham, 9100 Women and Infants Center, 1700 6th Ave S, Birmingham, AL 35233 (E-mail: jaten@peds.uab.edul).

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Abbreviations and Acronyms

AKI = acute kidney injury
BSI = bloodstream infection
CICU = cardiac intensive care unit
CPB = cardiopulmonary bypass
FFP = fresh frozen plasma
Ig = immunoglobulin
IVIG = intravenous immunoglobulin
OR = operating room
PD = peritoneal dialysis
POD = postoperative day
PRBC = packed red blood cell
SIRS = systemic inflammatory response syndrome
VAP = ventilator-associated pneumonia

and infants (4 potential time points per patient: pre-CPB, immediately post-CPB, and 24 and 48 hours post-CPB) and (2) review of the electronic records of the same 47 patients for postoperative Ig levels drawn for clinical purposes beyond 48 hours. Ig levels obtained after diagnosis of chylothorax, after treatment with intravenous immunoglobulin (IVIG), or while receiving extracorporeal membrane oxygenation were excluded from analysis. All other demographic, clinical, and laboratory data were obtained from our institutional clinical database. All laboratory values represent measurements on the day hypogammaglobulinemia was diagnosed, except where indicated.

Immunoglobulin and Cytokine Analysis

All plasma was stored at −80°C. All Ig concentrations were determined using the Fusion 5.1 analyzer (Ortho Clinical Diagnostics, Rochester, NY) in our institutional clinical laboratory. Interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor-α were assayed using a multiplex electrochemiluminescence detection method (MSD 2400 imager; Meso Scale Diagnostics, Gaitherburg, Md). Minimum sensitivities were 0.457 pg/mL for IL-1β, 0.018 pg/mL for IL-6, 0.10 pg/mL for IL-8, 0.809 pg/mL for IL-10, 0.780 pg/mL for IL-12, and 0.857 pg/mL for tumor necrosis factor-α.

Definitions

Because normal Ig concentrations for children with congenital heart disease have not previously been described, hypogammaglobulinemia for this study was defined as 2 SDs lower than the mean preoperative value of each respective Ig class. Modified inotrope score was used to reflect frequent use of arginine vasopressin[9]; milrinone was not included in the inotrope score calculation because of ubiquitous use.

Intraoperative and Postoperative Management

A dose of 10 mg/kg methylprednisolone was given at 8 and 1 hour before transfer to the operating room (OR); no intraoperative steroids were given. The CPB circuit was primed with 25% albumin, mannitol, sodium bicarbonate, and Normosol-R (Hospira Inc, Lake Forest, Ill). Fresh frozen plasma (FFP; 20 mL/kg) was added to the prime for patients weighing less than 5 kg. Packed red blood cells (PRBCs) were added to the CPB circuit to maintain the desired hematocrit based on physiologic characteristics. All patients received zero-balance ultrafiltration during CPB and single-pass ultrafiltration after CPB. Del Nido cardioplegia was used for aortic crossclamping. Postoperative management was protocolized to target age- and physiology-specific hemodynamic and respiratory goals via inotrope titration, colloid boluses, and ventilator adjustments, as described elsewhere.[10] We followed a fluid-restrictive protocol including 25% maintenance intravenous fluids during the first 24 hours and maximally concentrated infusions. Starting on postoperative day (POD) 1, oncotic pressure was maintained with 25% albumin (1 g/kg) to keep serum albumin at 3 g/dL or higher. Starting in January 2011, all complex neonatal repairs received prophylactic PD within 6 hours of admission to the cardiac intensive care unit (CICU) (median, 2.5 hours); all other patients began to receive furosemide infusions on POD 1 and received passive peritoneal drainage.

Statistical Analysis

SPSS, version 21 (IBM, Chicago, Ill), was used for all statistical analysis. Continuous variables not normally distributed were summarized as a median with interquartile range, with a group comparison performed using the Wilcoxon rank sum test. Continuous variables with a normal distribution were summarized as means with SDs and compared using the unpaired Student *t*-test. Trends of immunoglobulin classes through time were compared with paired *t*-test. Categorical data were compared using the Fisher exact test. The Spearman rank correlation was used to determine the relationship between FFP transfusion and post-CPB Ig levels. $P \leq .05$ was considered statistically significant. All statistical tests were 2-tailed. Because the minimum detectable IgA and IgM levels reported by our clinical laboratory are 7 and 4 mg/dL, respectively, we substituted all values of IgA "<7 mg/dL" with 6 mg/dL (5 occurrences) and all values of IgM "<4 mg/dL" with 3 mg/dL (33 occurrences) for statistical analysis.

RESULTS

There were 150 stored plasma Ig results from the first 48 hours and 22 additional results beyond 48 hours; each sample analysis included IgA, IgG, and IgM. As a result of random depletion from the previous study, 38 time points had inadequate quantities of stored plasma available for Ig analysis; these were well balanced among study groups and time points. Sample contribution from each time point can be seen in Table 1. A total of 30 subjects had complete data, 16 of whom had hypogammaglobulinemia and 14 of whom had normal IgG at all time points. The median age and weight were 7 days and 3.2 kg, respectively. Other demographic data are presented in Table 2.

Immunoglobulin Concentrations

Table 1 shows mean and median Ig concentrations through the first 48 hours after CICU admission. There were 25 patients (53%) who had low post-CPB IgG (<248 mg/dL). In the 30 subjects for whom complete analysis of the initial 48 hours was possible, there was a 57% reduction (95% confidence interval, 45%-69%) in preoperative IgG levels at 24 hours and a 64% reduction (95% confidence interval, 52%-76%) at 48 hours (Figure 1). IgG remained lower than preoperative values for up to 7 postoperative days. For the 22 samples drawn for clinical purposes beyond 48 hours, the mean IgG concentration on POD 3 was 243 mg/dL (n = 7); POD 4, 236 mg/dL (n = 4); POD 5, 236 mg/dL (n = 3); POD 6, 270 mg/dL (n = 5); and POD 7, 221 mg/dL (n = 3). Both IgM and IgA levels were higher immediately after CPB and trended toward preoperative values over time (Figure 1). Five patients had low IgA and 4 patients had low IgM at some point post-CPB; all of these patients had