Time Course of C-Reactive Protein and Inflammatory Mediators after Neonatal Surgery

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Objective To characterize the perioperative course of C-reactive protein (CRP) and inflammatory mediators in neonates ≤44 weeks' corrected gestational age.

Study design Prospective study of CRP and inflammatory mediators interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor-α in 55 neonates undergoing thoracic or abdominal surgery.

Results In the absence of infection, CRP increased after surgery, peaking on post-operative day 2. The perioperative patterns of CRP differed by diagnosis and inflammatory state. Surgery alone did not cause an increase in CRP because in 13 of 55 infants (24%), CRP remained <1.0 mg/dL at all time points. For thoracic procedures, patent ductus arteriosus ligation showed the least post-operative increase in CRP, and patients undergoing repair of congenital diaphragmatic hernia or tracheoesophageal fistula had a greater response. Abdominal procedures with low CRP response included repair of imperforate anus and pyloric stenosis, while gastroschisis repair and bowel reanastomosis after necrotizing enterocolitis were accompanied by a robust CRP response. IL-6 concentrations peaked on post-operative day 1 and correlated with the post-operative day 2 CRP peak ($r = 0.398$, $P = .004$). The additional inflammatory mediators measured were not informative.

Conclusions The range and time course of perioperative CRP differ by diagnosis. Serial measurements may be more informative than CRP magnitude. *(J Pediatr 2011;159:121-6)*.

Critically ill neonates who undergo surgery are at risk for infections because of skin and mucosal disruption, surgical instrumentation, or installation of foreign bodies. Detection of post-operative infections in neonates is problematic because signs of infection can be subtle and difficult to distinguish from surgical trauma-induced inflammation or fever unrelated to infection.[1,2] Post-operative blood cultures can be misleading because they may be falsely negative due to insufficient sample volume or antibiotic exposure, or falsely positive due to contamination.[3,4] Consequently, adjunctive tests such as C-reactive protein (CRP) or inflammatory mediators are being considered to help evaluate post-operative infection in neonates.

CRP is particularly promising. This test is widely available, inexpensive, quick, requires only 100 μL of blood, and it has a negative predictive value of 99% in term and near-term nonsurgical neonates. Serial CRP measurements for 48 hours after initial concern are most helpful because early CRP values may be normal.[5-9] An elevated CRP does not necessarily predict infection because CRP is an acute-phase reactant produced by the liver in response to inflammatory stimuli, mediated by interleukin (IL)-6 and other inflammatory mediators.[10,11] The positive predictive value of CRP for proven sepsis is low.[5-9] Although semiquantitative assessments of serial CRP measured in post-operative neonates have been reported,[12] normative data regarding the time course and response range after surgery is incomplete. It is unknown whether surgery alone stimulates a sufficient acute-phase response to confound the value of acute-phase reactants for diagnosis of post-operative infection in neonates.

To address these issues, we conducted a prospective clinical study to characterize the time course of perioperative changes in CRP and inflammatory mediators in neonates undergoing abdominal and thoracic surgical procedures. We stratified patients on the basis of surgical diagnosis to evaluate whether there were differential patterns of response. This report provides the range and time course of post-operative CRP fluctuations in neonates by surgical diagnosis.

Methods

Patient Population

Infants admitted to the neonatal intensive care units at Seattle Children's Hospital and the University of Washington Medical Center for possible surgical procedures

CDH	Congenital diaphragmatic hernia
CRP	C-reactive protein
IL	Interleukin
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
TEF	Tracheoesophageal fistula
TNF	Tumor necrosis factor

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between March 2008 and February 2010 were assessed for inclusion in the study. Eligible patients were ≤44 weeks' corrected gestational age and scheduled for an abdominal or thoracic surgical procedure. Patients were excluded for known infection before surgery, liver dysfunction, chromosomal or congenital anomalies, or recent extracorporeal membrane oxygenation. Patients were also excluded when consent could not be obtained because the parents were not fluent in reading English. This study was approved by the institutional review board.

Blood was collected at baseline (before surgery) and on post-operative days 1, 2, and 3. VITROS Chemistry Products CRP slides (Ortho-Clinical Diagnostics, Inc, Raritan, New Jersey) were used for all CRP measurements, with a normal range of <0.8 mg/dL. Residual sera were stored at –70°C until batched analysis. Serum concentrations of IL-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α were measured using the Luminex xMAP platform with Milliplex high-sensitivity inflammatory cytokine plates (Millipore, Temecula, California).[13]

For each infant, the surgical procedure, preoperative and post-operative diagnoses, surgical findings, and complications were recorded. Demographic data included gestational age at birth, postnatal age and corrected gestational age at the time of surgery, sex, birth weight, and weight at the time of surgery. Concurrent medical diagnoses were recorded, including respiratory distress syndrome, bronchopulmonary dysplasia, infections, and intraventricular hemorrhage. Use of corticosteroids (dexamethasone, hydrocortisone, and prednisone) and antibiotics was noted. Nonstudy labs obtained as part of routine medical care from one day before surgery to 4 days after surgery were analyzed: WBC, ANC, percentage of neutrophils and bands, platelet count, and cultures of blood, urine, cerebrospinal fluid, and tracheal aspirates.

Statistics

Mixed-model ANOVA (for repeated and between-group measures) and post hoc testing were performed. SPSS software (SPSS Inc, Chicago, Illinois) was used. Data are expressed as mean values and may include SEM and number of subjects (n). An α criterion of $P < .05$ was used with two-tailed testing.

Results

One hundred twenty-eight patients ≤44 weeks' corrected gestational age were admitted for surgery; 69 were excluded on the basis of inclusion and exclusion criteria, and 4 were excluded because the sample processing was confounded by delay.[14] Thus, a total of 55 patients were included in this study, one of whom had a post-operative infection and was considered separately. Table I shows weights and ages for all subjects, at birth and at surgery, separated by surgery type. Abdominal surgeries included gastroschisis repair, intestinal reanastomosis after necrotizing enterocolitis (NEC), imperforate anus repair, bladder exstrophy, pyloric stenosis, omphalocele, duodenal duplication cyst, duodenal atresia, jejunal atresia, and perforated Meckel diverticulum. Thoracic surgeries included repair of congenital diaphragmatic hernia (CDH), patent ductus arteriosus (PDA), tracheoesophageal fistula (TEF), naso-pharyngeal mass, branchial pouch remnant, bronchopulmonary sequestration, and coarctation of the aorta. Patient characteristics varied by diagnosis: Those with gastroschisis, imperforate anus, TEF and CDH were generally of near term or term gestation and underwent surgical repair in the first week of life. In contrast, patients undergoing PDA ligation or intestinal reanastomosis after NEC tended to be <1000 g and 28 weeks' gestation at birth, and their surgeries occurred later in life.

Table II lists the mean ± SEM for CRP and inflammatory mediators measured from all infants before and after surgery. CRP increased from baseline to peak on post-operative day 2, declining by post-operative day 3 for all noninfected infants. The pattern of CRP increase and fall differed by diagnosis. Figure 1, A shows the time course for individual patients undergoing abdominal surgery grouped by diagnosis, and Figure 1, B shows similar groupings for patients undergoing thoracic surgery. One patient who underwent PDA ligation had *Pseudomonas tracheitis* after surgery and showed a marked elevation in CRP (shown by *dotted line*). In contrast to CRP, IL-6 concentrations peaked on post-operative day 1. The post-operative day 1 IL-6 peak values correlated with the post-operative day 2 CRP peak values ($r = 0.398$, $P = .004$). There were no significant changes over time in the additional inflammatory mediators in Table II, therefore post hoc testing was not performed.

To determine whether a surgical procedure alone was sufficient to cause a rise in CRP, we asked whether any patients undergoing surgery did not show a post-operative increase in CRP. In 24% (13 of 55 patients), CRP was <1.0 mg/dL at all four time points. These surgeries included both thoracic and abdominal procedures, with repair of CDH, PDA, pyloric stenosis, duodenal and jejunal atresia, and omphalocele. Surprisingly, this group included one patient who presented with free air and intestinal perforation caused by Meckel diverticulum, but this probably occurred before gut colonization.[15] A post hoc comparison of data from patients with no known source of inflammation (n = 24) to those with presumed inflammation (n = 30) was then performed. The groups of patients included in the "presumed inflammation" group and the rationale for inclusion were as follows: (1) those with gastroschisis were included because of the inflammatory "peel" present on the bowel of these infants; (2) those with foreign bodies placed at the time of surgery (chest tube or polypropylene and polytetrafluoroethylene mesh (W.L. Gore & Associates, Flagstaff, Arizona) were chosen because of the presumed inflammatory response to a large foreign body; (3) those with documented abscess or inflamed mass; and (4) patients who underwent bowel reanastomosis after NEC were included because they all required extensive dissection to remove post-NEC adhesions. Figure 2 compares the CRP measures between uninflamed neonates and those with presumed inflammation, based on diagnosis or