Relationship Between Antiinflammatory Cytokine Interleukin-10 and Lactate Concentrations in Neonates Undergoing the Arterial Switch Operation

Kyrylo Chasovskyi, MD, PhD, Volodymyr Zhovnir, MD, PhD, Ganna Vorobiova, MD, PhD, and Illya Yemets, MD, PhD

Departments of Perfusiology, Surgery, Immunology, Intensive Care, and Anesthesiology, Ukrainian Children's Cardiac Center, Kyiv, Ukraine

Background. **The aim of this study was to evaluate the relationship between antiinflammatory cytokine interleukin (IL)-10 production and perioperative lactate concentrations and their impact on postoperative outcomes in neonates undergoing the arterial switch operation (ASO).**

Methods. **Between August 2010 and August 2012, 80 neonates with transposition of the great arteries (TGA) were enrolled. Serum IL-10 levels were measured immediately before and after cardiopulmonary bypass (CPB) on the first, third, and seventh days. Perioperative clinical data were collected prospectively.**

Results. **Patients underwent the ASO at a median age of 72 hours (4–144 hours). We found that serum IL-10 levels significantly correlated with a prolonged intensive care unit (ICU) length of stay ($r = 0.3$; $p = 0.020$) and duration of ventilation ($r = 0.3$; $p = 0.017$). Serum IL-10 levels on the first day after the surgical procedure had predictive value for a prolonged ICU stay (defined as an ICU stay >6 days postoperatively) by receiver operator curve analysis, with an area under the receiver operating characteristic (ROC) curve of 0.65 ($p = 0.045$). Logistic regression modeling indicated that serum lactate level ($\beta = 2.7$; $p = 0.027$), age at operation ($\beta = -4.0$; $p = 0.007$), and the nature (autologous or allogeneic) of blood products ($\beta = -3.5$; $p = 0.030$) used during CPB affected serum IL-10 levels. The strongest predictor of increased IL-10 on the first day after operation was a serum lactate level greater than 3 mmol/L measured after the surgical procedure on admission to the ICU, recording an odds ratio of 15.31. Serum lactate levels after operation and at admission to the ICU positively correlated with a prolonged ICU stay ($r = 0.4$; $p = 0.007$).**

Conclusions. **Elevated lactate levels are associated with increased IL-10 production on the first postoperative day. Excessive production of IL-10 on the first day after the surgical procedure is associated with a prolonged ICU stay.**

(Ann Thorac Surg 2015;■:■–■)

Cardiopulmonary bypass (CPB) is known to trigger a global inflammatory response. Mechanisms of inflammatory activation during CPB include contact cell activation, mechanical shear stress, ischemia-reperfusion injury, heparin-protamine interactions, hypotension, hemodilution with relative anemia, and blood product administration [1]. Neonates are the most susceptible to an inflammatory response to CPB for several reasons, including the adaptive status of the immune system, high metabolic demands, the relatively high volume of the extracorporeal circuit, and immaturity of all organ systems with altered homeostasis [1, 2].

Numerous studies have demonstrated that open heart operations alter production of specific proinflammatory and antiinflammatory cytokines [3–5]. Cytokines are both participants in inflammation and markers of the ongoing response. Although the antiinflammatory cytokines limit the extent of the inflammatory response and begin to restore homeostasis, an excessive antiinflammatory cytokine response may follow an excessive proinflammatory response and result in immunocompomise [6]. Moreover, in addition to significant inflammatory response, many patients experience metabolic acidosis and increased serum lactate levels during and just after CPB [7]. Previous studies suggest that lactate levels are significantly related to adverse outcomes after open heart operations [7, 8]. Therefore we investigated the relationship between antiinflammatory cytokine (interleukin [IL]-10) production and lactate levels in neonates who underwent an arterial switch operation (ASO). The purpose of this study was to measure production of IL-10 in neonates who underwent open heart operations to test the theory that significantly increased IL-10 production is associated with increased perioperative lactate levels and is related to impaired outcomes.

Patients and Methods

The Institutional Review Board of the Ukrainian Children's Cardiac Center approved this study. Written consent was obtained from parents of all patients.

Accepted for publication Sept 28, 2015.

Address correspondence to Dr Chasovskyi, Ukrainian Children's Cardiac Center, Chornvola St 28/1, Kyiv 01135, Ukraine; e-mail: kchasovskiy82@gmail.com.

Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.09.087

Patients

This was an ancillary study to our previously published study of the use of autologous umbilical cord blood (UCB) transfusion in neonates with transposition of the great arteries (TGA) [9, 10]. We continued evaluation of the benefits of autologous UCB transfusion during neonatal open heart operations. Between August 2010 and August 2012, 80 neonates with TGA were enrolled in this study.

Anesthetic and Perfusion Technique

A standardized narcotic anesthetic was used—including fentanyl, vecuronium, and sevoflurane—and maintenance was with fentanyl and morphine sulfate infusion. Heparin (300 IU/kg) was administered and CPB was instituted using ascending aortic and bicaval cannulation. CPB was performed using a roller pump with a miniaturized circuit (110–140 mL priming volume) without an arterial filter. Full-flow CPB was used at 200 mL/kg/min and alpha-stat pH management was between 28°C and 36°C. The hematocrit target during perfusion was set at a minimum level of 25%. Mean arterial pressure during CPB was maintained at a level of 30 to 50 mm Hg and the central venous pressure was between –5 and 0 mm Hg. Diastolic arrest was achieved with cold crystalloid cardioplegia (Custodiol HTK Solution; Essential Pharmaceuticals, LLC, Ewing, NJ). Postoperative management occurred in an intensive care unit (ICU) according to standardized unit protocols.

Blood Management

Our procedure, since September 2009 in neonates with prenatally diagnosed (dextro) d-TGA, is to harvest and transfuse autologous UCB during the operation [9]. In this study, 36 (45%) neonates received an autologous UCB transfusion, and 44 (55%) neonates received fresh (stored <6 days) donor red blood cells (RBCs) for priming the CPB circuit and for perioperative transfusions.

Study Procedures

Whole blood samples were obtained from indwelling arterial or central venous catheters after anesthetic induction but before skin incision, as well as on the first, third, and seventh days after operation. The dynamics of IL-10 concentrations were examined by enzyme-linked immunosorbent assay. Detailed clinical data were extracted from medical records and our institutional database. Preoperative data included diagnosis, demographics, mechanical ventilation, and standard clinical laboratory data. Intraoperative data included CPB and ischemic times, blood products administered, lactate concentration, and hematocrit value. Postoperative variables included duration of intubation, length of stay in the ICU and hospital stay, and lactate concentration. Data were collected on intra- and postoperative blood transfusions, including autologous UCB and donor blood products.

Statistical Methods

All data were checked for normality of distribution and normalized using log-transformation when applicable. Data compared between groups were analyzed using Student's t test or the Mann-Whitney U test. Pearson's correlation (r) or Spearman's rank (R) correlation was performed to examine the relationship between continuous variables. The area under the receiver operating characteristic (ROC) curve was calculated to test the discriminatory power of IL-10 to predict a prolonged length of stay in the ICU. Binomial logistic regression was used for further examination of the relationship between perioperative variables and elevated IL-10 concentration on the first day after the surgical procedure. Statistical analysis was done with IBM SPSS Statistics, version 21.0 (SPSS, Inc, Chicago, IL). A p value less than 0.05 was considered statistically significant.

Results

Eighty neonates with d-TGA were enrolled in this study. Diagnoses, demographic data, and perioperative variables are reported in Table 1. Significant changes in the concentrations of IL-10 were seen postoperatively in comparison with baseline values (Fig 1). Median IL-10 concentrations increased on the first day after operation (3.7 versus 8.2 pg/mL; $p < 0.001$). On the third day after operation, IL-10 levels decreased from a median of 8.2 pg/mL to 4.4 pg/mL ($p < 0.001$). On the seventh day after operation, IL-10 levels returned to baseline (3.7 pg/mL). Correlational analysis of the relationship between perioperative IL-10 concentrations and selected variables is

Table 1. Demographic and Perioperative Characteristics (N = 80)

Demographic variables	Median (25%–75%)
Age (h before operation)	72 (4–144)
Weight (kg)	3.4 (3.03–3.8)
Diagnoses n (%)	
d-TGA/intact ventricular septum	61 (76.3)
d-TGA/ventricular septal defect	18 (22.5)
d-TGA/coarctation of the aorta	1 (0.2)
Preoperative variables	
Length of stay in ICU, d	0 (0–3)
Intubated, n (%)	18 (22.5)
Rashkind procedure, n (%)	55 (68)
Intraoperative variables	
Total support time (min)	150 (137–179)
Ischemic time (minutes)	79 (71–87)
Highest lactate level during CPB (mmol/L)	3 (1–5)
Postoperative variables	
Length of stay in ICU (d)	6 (5–8)
Time of intubation (h)	48 (34–68)
Hospital stay (d)	16 (14–22)

CPB = cardiopulmonary bypass; d-TGA = dextro transposition of the great arteries; ICU = intensive care unit.