Impact of Operative and Postoperative Factors on Neurodevelopmental Outcomes After Cardiac Operations

The International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators*

Background. Neurodevelopmental disability is common after operations for congenital heart defects. We previously showed that patient and preoperative factors, center, and calendar year of birth explained less than 30% of the variance for the Psychomotor Development Index (PDI) and the Mental Development Index (MDI) of the Bayley Scales of Infant Development-Second Edition. Here we investigate how much additional variance in PDI and MDI is contributed by operative variables and postoperative events.

Methods. We analyzed neurodevelopmental outcomes after operations with cardiopulmonary bypass at age 9 months or younger between 1996 and 2009. We used linear regression to investigate the effect of operative factors (age, weight, and cardiopulmonary bypass variables) and postoperative events on neurodevelopmental outcomes, adjusting for center, type of congenital heart defect, year of birth, and preoperative factors.

Results. We analyzed 1,770 children from 22 institutions with neurodevelopmental testing at age 13.3 months (range, 6 to 30 months). Among operative factors, longer total support time was associated with lower PDI and MDI ($p < 0.05$). When postoperative events were added, use of either extracorporeal membrane oxygenation or ventricular assist device support, and longer postoperative length of stay were associated with lower PDI and MDI ($p < 0.05$). Longer total support time was not a significant predictor in these models. After adjusting for patient, preoperative, intraoperative, and postoperative factors, measured intraoperative and postoperative factors accounted for 5% of the variances in PDI and MDI.

Conclusions. Operative factors may be less important than innate patient and preoperative factors and postoperative events in predicting early neurodevelopmental outcomes after cardiac operations in infants. Neurodevelopmental outcomes improved over calendar time when adjusted for patient and medical variables.

(Ann Thorac Surg 2016;102:843–9)

Neurodevelopmental (ND) disabilities are the most common, and, potentially, the most damaging, sequelae of congenital heart defects (CHDs) [1–7]. We recently analyzed individual participant data from studies of children with repaired CHDs who were evaluated with the Bayley Scales of Infant Development, Second Edition (BSID-II), to determine the effect of innate patient and preoperative factors on ND outcomes over time after adjusting for center and cardiac class [1, 8]. Risk factors for a lower Psychomotor Development Index (PDI) were lower birth weight, Caucasian race, and presence of a genetic/extracardiac anomaly and for a lower Mental Development Index (MDI) were lower birth weight, male gender, less maternal education, and presence of a genetic/extracardiac anomaly. PDI and MDI both improved significantly over time (PDI: 0.39 points/year; MDI: 0.38 points/year) after adjustment for patient and preoperative factors.

Our earlier analysis did not investigate the effect of cardiopulmonary bypass (CPB) management strategies or postoperative variables, which have been shown to be potentially important modifiers of ND outcomes in previous studies [1–7]. Here, we used the same pooled individual participant data to investigate the effect of CPB

Accepted for publication May 3, 2016.

Presented at the Fifty-second Annual Meeting of the Society of Thoracic Surgeons, Phoenix, AZ, January 23–27, 2016.

*A complete list of the International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators appears at the end of this article.

Address correspondence to Dr Gaynor, The Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104; email: gaynor@email.chop.edu.

The Supplementary Tables can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2016.05.081] on http://www.annalsthoracicsurgery.org.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.05.081

Abbreviations and Acronyms

BSID-II = Bayley Scales of Infant Development, Second Edition
CHD = congenital heart disease
CI = confidence interval
CPB = cardiopulmonary bypass
CPR = cardiopulmonary resuscitation
DHCA = deep hypothermic circulatory arrest
ECMO = extracorporeal membrane oxygenation
HLHS = hypoplastic left heart syndrome
LOS = length of stay
MDI = Mental Development Index
ND = neurodevelopmental
PDI = Psychomotor Development Index
RCP = regional cerebral perfusion
TGA = dextro-transposition of the great arteries
TOF = tetralogy of Fallot
VAD = ventricular assist device

management factors and postoperative events on the ND outcomes, including the effect on temporal trends over the 14-year interval.

Material and Methods

Eligibility for inclusion, classification of heart disease, and the analytic data set were previously described [1]. Inclusion criteria were cardiac operation using CPB at age 9 months or younger, enrollment in a clinical trial or observational study with date of operation between 1988 and 2009, ND evaluation between age 6 and 30 months; and data available on patient, operative management, and postoperative variables [2, 7, 9–16]. Each institution obtained approval or exemption from its Institutional Review Board.

The sample was restricted to patients assessed using the BSID-II, a standardized assessment of cognitive and motor development for children aged 1 through 42 months [8]. The PDI, our primary outcome, assesses motor function, whereas the MDI, our secondary outcome, assesses cognitive functions. The mean $\pm$ standard deviation is 100 ± 15 in the normative population for both scores. Motor skills (PDI) are usually more affected in survivors of cardiac operations than are cognitive abilities (MDI) [13, 17].

Investigators used cardiac diagnosis to code patients into one of four categories shown to predict perioperative death:

- class I: 2 ventricles with no aortic arch obstruction;
- class II: 2 ventricles with aortic arch obstruction;
- class III: 1 ventricle without arch obstruction; and
- class IV: 1 ventricle with arch obstruction [18].

Anomalies were classified as definite genetic anomalies, suspected genetic anomalies or major extracardiac anomalies, or absent (normal). Patients in whom the presence or absence of an anomaly was not noted were classified as normal.

Statistical Analysis

Primary analyses examined the relationships of PDI and MDI with operative management and postoperative factors using linear regression adjusting for center, cardiac class, year of birth, and patient and preoperative factors shown to be significantly predictive in this sample (PDI: birth weight, race, genetic anomaly; MDI: birth weight, sex, maternal education, genetic anomaly) [1]. Candidate operative management predictors included neonatal status (age at first operation $\leq$30 days), weight at operation, cooling duration, pH gas management, lowest nasopharyngeal temperature, lowest hematocrit, and durations of total support time and its components, including CPB, deep hypothermic circulatory arrest (DHCA), and regional cerebral perfusion (RCP). Predictors were screened to identify associations with PDI or MDI at the level of p of less than 0.20 after the adjustments outlined. Predictors meeting this criterion were included in stepwise backward elimination in which p of less than 0.05 served as the retention criterion. The components of total support time were also considered in additional analyses.

Analyses of postoperative factors followed the same methods but were also adjusted for significant operative management predictors. Candidate postoperative predictors included use of extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD), use of cardiopulmonary resuscitation (CPR), clinical seizure, postoperative hospital length of stay (LOS; quartiles), and additional operation(s) with CPB. Candidate predictors that had more than 25% with missing values were considered in separate analyses.

Differences among CHD subgroups were assessed using χ^2 and Kruskal-Wallis tests. Subgroup analyses were performed based on three types of CHD: dextro-transposition of the great arteries (TGA) with intact ventricular septum or ventricular septal defect, tetralogy of Fallot, with or without pulmonary atresia, and hypoplastic left heart syndrome. Standardized mean scores represent predicted PDI and MDI adjusting for center, cardiac class, and other components of the full postoperative model at the mean value of the covariates. Analyses were performed using SAS 9.3 software (SAS Institute Inc, Cary, NC).

Results

Characteristics of the full sample and the diagnostic subgroups are provided in Table 1 [1]. Our cohort of 1,770 patients from 22 institutions from 6 countries was assessed with the BSID-II at age 13.3 months (range, 6 to 30 months). As part of their initial CPB operative course, 52.8% underwent DHCA and 16.3% underwent RCP. Median postoperative LOS was 15 days (range, 0 to 286 days).

Operative Management Factors

After adjusting for center, cardiac class, year of birth, and significant patient and preoperative risk factors, significant predictors of lower PDI included longer total support ($p = 0.005$) and CPB ($p = 0.03$) durations. The final PDI