RESEARCH PAPER

Early Neurodevelopmental Outcomes After Corrective Cardiac Surgery In Infants

Ritchie Sharon Solomon[1], Tanuja Sasi[2], Abish Sudhakar[1], Raman Krishna Kumar[1] and Balu Vaidyanathan[1]

From Departments of [1]Pediatric Cardiology and [2]Pediatrics, Amrita Institute of Medical Sciences, Amrita University, Kochi, Kerala, India.

Correspondence: Dr Balu Vaidyanathan, Clinical Professor, Pediatric Cardiology, Amrita Institute of Medical Sciences, Amrita University, Kochi, Kerala 682 041, India. baluvaidyanathan@gmail.com

Received: March 10, 2017; Initial review: June 19, 2017; Accepted: February 07, 2018.

Objective: To assess neurodevelopmental status in Indian infants undergoing corrective surgery for congenital heart disease (CHD) and to analyze factors associated with neurodevelopmental delay.

Design : Cross-sectional study.

Setting: Tertiary-care pediatric cardiology facility.

Participants: Consecutive infants undergoing corrective surgery for CHD (January 2013 –December 2014). Palliative procedures, and patients with known genetic syndromes were excluded.

Main outcome measures: Neurodevelopmental evaluation 3 months, and one year after surgery using Developmental Assessment Scales for Indian Infants (DASII); scores were categorized as delayed if ≤70.

Results: Of the 162 children enrolled, delayed PDI and MDI scores were observed in 33.5% and 19.6% of patients at 3 months, respectively; this reduced to 14.5 % on 1-year follow-up. On multivariate analysis, delayed PDI outcome at one year was predicted by early term birth and one-year postoperative head circumference Z-score <–2. Delayed MDI was associated with higher mean perfusion pressure on cardiopulmonary bypass. Cardiac diagnosis and peri-operative factors did not impact neurodevelopmental outcomes.

Conclusions: Neurodevelopmental status is delayed in 14.5% of infants one year after corrective infant heart surgery.

Keywords: *Congenital heart disease, Neuromotor delay, Outcome*

Outcomes of surgery for congenital heart disease (CHD) have been improving in recent times [1]. Studies from developed countries have reported higher prevalence of neurological and speech impairments as well as deficits in attention and executive functions on follow-up [2-6].

There is limited information about neurodevelopmental outcomes after surgery for CHD from low- and middle-income countries (LMICs). Of late, many centres from LMICs have started performing corrective surgical procedures in neonates and infants with CHD, with outcomes comparable to those from developed nations [7,8]. However, the demographic profile and pre-operative characteristics are very different in LMICs and these could significantly impact long-term outcomes [7-12]. An analysis of Indian children with uncorrected CHD has shown that they are at increased risk of developmental delay [13]. These can have a significant impact on neurodevelopmental outcomes despite high-quality surgical expertise and post-operative intensive care.

This prospective study from a tertiary-care pediatric cardiac center examines the short term neuro-developmental outcomes in infants undergoing corrective surgery for CHD.

Methods

This cross-sectional study was conducted in a tertiary-care pediatric cardiology facility in Kerala, from January 2013 to December 2014. Consecutive patients (<1 year) undergoing corrective surgery for CHD were included. Exclusion criteria included: (*i*) palliative operations, (*ii*) Genetic syndromes, (*iii*) preterm babies (<37 weeks gestation), (*iv*) small for gestational age (birth weight <10th percentile/<–2SD), and (*v*) confirmed neurological or developmental abnormalities. The study protocol was approved by the Institutional ethics committee and written informed consent was obtained from all parents.

Demographic details included age at surgery, sex, birth weight, gestational age (early term 37- 39 weeks vs. full term ≥39 weeks), mode of delivery, and

socioeconomic class as per modified Kuppusamy classification [14]. Anthropometric data (weight, height, head circumference and weight/height) were taken pre-operatively and at follow-up. Z-scores were calculated based on World Health Organisation (WHO) normograms for age and sex with values <–2 considered as abnormal.

Cardiac diagnosis with the pre-operative risk score based on the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) classification was recorded. Details of prenatal diagnosis, delivery and mode of transport to the cardiac center (monitored/unmonitored) were recorded. Duration of ventilation and prostaglandin (PGE1) infusion (hours), ICU and hospital stay (days), hematocrit, sepsis (culture positive/clinical), oxygen saturation and nature of the surgical procedure (planned/urgent) were recorded.

Duration of cardiopulmonary bypass (CPB), aortic cross clamp (ACC) and total circulatory arrest (minutes), mean perfusion pressure during CPB (mm Hg), minimum hematocrit, lowest temperature, modified/continuous ultrafiltration, major hypoxic events (PaO2 <55 mm Hg), cardiac arrest, arrhythmia with hemodynamic compromise, air embolism and need for re-institution of CPB were noted. The CPB flow rates and mode of ultra-filtration were based on surgical preferences. Direct cerebral vascular monitoring was not done.

Duration of mechanical ventilation and inotropic support (hours), ICU and hospital stay (days) were noted. Delayed sternal closure, re-intubations, pulmonary hypertension (PH) crisis, cardiac arrests requiring resuscitation, focal neurological deficits, post-operative sepsis and seizures were noted. Prolonged ventilation, and prolonged ICU stay were defined as >48 hours and >7 days, respectively.

All patients were followed up 3 months and 1 year after surgery. Neurodevelopmental assessment was done using Developmental Assessment Scale for Indian Infants (DASII), which is considered to be the best formal test in Indian context [15]. Using DASII, the psychomotor developmental index (PDI) and mental developmental index (MDI) were calculated and categorized as delayed when scores were ≤70 (≤–2 SD). Early intervention program was initiated if the PDI and MDI were delayed after the first follow-up assessment.

Statistical analysis: Student's *t* test was used to compare continuous risk factors by normal and delayed group. Chi-square test was used to find the association between demographic and perioperative categorical factors by PDI and MDI (delay) category. One way ANOVA was used to compare the PDI and MDI by RACHS category. Multivariate binary logistic regression analysis (stepwise) was used to estimate the Odds Ratio with 95% Confidence Intervel and adjusting for potential confounding variables. The cut-off point for statistical significance was set an alpha level of 5%. Statistical analysis was done using IBM SPSS 20.0 (SPSS Inc, Chicago, USA).

RESULTS

Of the 162 infants (92 males) included, 52 (32.1%) were neonates. There was no in-hospital mortality. Four patients (2.4%) died on follow-up; 3 had residual cardiac issues, and in one cause of death was unknown **(*Fig*. 1).** RACHS category 1 and 2 constituted 59.3% (96) of the surgical procedures **(*Web Table* I)**. Prenatal diagnosis was made in 4.3% of patients.

The distribution of acyanotic (80, 49.4%) and cyanotic CHD were similar. Preoperative weight, height, head circumference were abnormal in 110 (67.9%), 48 (29.6%) and 60 (37%) children, respectively. Preoperative ICU care was needed in 56 (36.4%) with a median stay of 4 (1-30) days; 15 (9.3%) had pre-operative sepsis. The median age at surgery was 60 days (2-365).

Major intraoperative complications occurred in 10 infants (6.2%). One had a major hypoxic event while 9 patients (5.5%) had arrhythmias with hemodynamic compromise. Re-institution of CPB was required in 7 infants (4.3%). The median CPB and ACC time were 109 min (41-457) and 58 min (10-274), respectively **(*Web Table* I).** The mean (SD) hematocrit and perfusion pressure on CPB was 28.4 (3.11) %and 38.4 (4.11) mm Hg. The median duration of postoperative ventilation and inotrope was 42 (3 - 552) and 72 (2 - 432) hours, respectively. Delayed sternal closure was done in 8 infants (4.9%). Mean (SD) postoperative ICU stay was 7.3 (5.41) days. Postoperative sepsis occurred in 32 infants (19.8%). Re-intubation was required in 15 (9.3%) infants.

Anthropometric indices improved on one-year follow-up with abnormal weight for age and weight/height Z scores in 23% (35) and 16.4% (25), respectively. Height-for-age and head circumference Z scores were abnormal in 27.6% (42) and 23% (35), respectively.

At three months after corrective surgery, delayed PDI was seen in 53 (33.5%) and mean (SD) PDI score was 81.2 (33.02); this improved to 92.4 (26.02) at one-year follow-up (22, 14.5% delayed). On univariate analysis, factors associated with delayed PDI at one-year follow-up included gestational age <39 weeks, weight and head

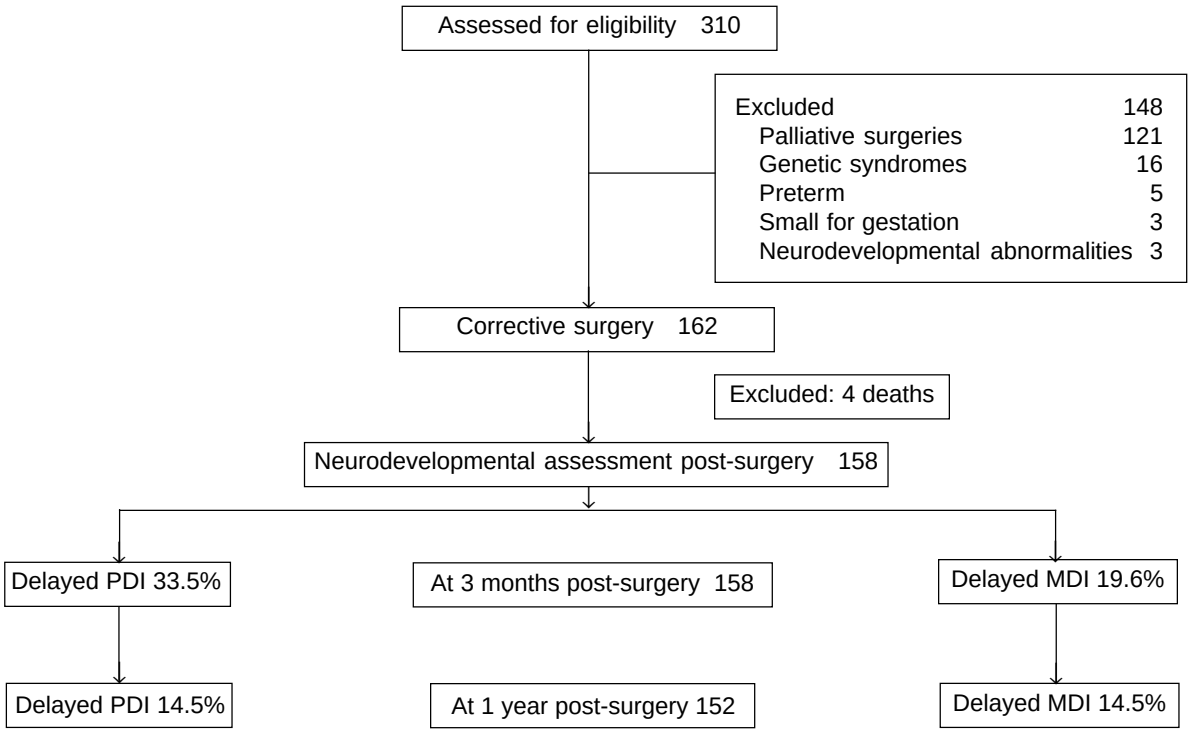

FIG. 1 *Flow of participants in the study.*

circumference *Z*-score <–2 on follow-up, postoperative ventilation >48 hours, postoperative ICU stay >7 days and longer duration of postoperative inotrope use. Lower mean PDI score was associated with weight (*P*=0.02) and head circumference Z-score < -2 (*P*=0.009) at one year follow up.

At three months after corrective surgery, delayed MDI was seen in 31 (19.6%) and mean (SD) MDI score was 90.0 (27.17); this improved to 96.1 (26.05) at one-year follow-up (22, 14.5% delayed). On univariate analysis, factors associated with lower mean MDI scores at one-year follow-up were gestational age <39 weeks (*P*<0.001) and preoperative weight *Z*-score <-2 (*P*=0.03).

TABLE I MULTIVARIATE REGRESSION ANALYSIS OF PREDICTORS OF DELAYED PDI AND MDI

Variables	*OR (95% CI)*	*P value*
PDI outcome at 1 year follow-up		
Gestational age < 39 wk	7.51 (1.61-35.03)	0.01
[#]Head circumference <–2 Z score	5.39 (1.19-24.47)	0.02
MDI outcome at 1 year follow up		
Mean perfusion pressure on CPB	1.13 (1.00-1.27)	0.05

CPB: Cardiopulmonary bypass; [#]at 1 year post-surgery.

On multivariate regression analysis, the variables associated with delayed PDI outcome at one year follow-up were gestational age <39 weeks and one year postoperative head circumference Z score <-2 **(*Table* I)**. Delayed MDI at one year was associated with higher mean perfusion pressure on CPB (*P* = 0.05).

DISCUSSION

We analyzed the short-term neurodevelopmental outcomes in Indian infants undergoing corrective surgery for CHD. Though the PDI and MDI scores improved on one-year follow-up, 14.5% of patients continued to have delay. The motor skills was more affected than the mental skills and cognitive function at both points of time. Patient-specific constitutional factors like early term birth and head circumference on follow-up were associated with neurodevelopmental outcomes rather than peri-operative factors or cardiac diagnosis.

Formal developmental assessment by DASII was not done pre-operatively and it is possible that subtle neurological abnormalities which could have impacted outcomes, and pre-existing developmental delay were missed. We did not have a cohort of non-CHD or unoperated infants for comparison of developmental indices.

WHAT IS ALREADY KNOWN ?

- Children with congenital heart disease are at risk for neuro-developmental delay even after corrective surgery.

WHAT THIS STUDY ADDS?

- Patient-specific factors like early term birth and head circumference at one-year after surgery predict neurodevelopmental outcomes than peri-operative factors or the cardiac diagnosis in children undergoing cardiac surgery for congenital heart disease.

The patterns of developmental delay are in accordance with findings of previous studies affecting psychomotor domains more than mental milestones [3,6,13,17]. Several studies have stated that patient-specific factors are important determinants of neurodevelopmental outcome compared to peri-operative factors [2,3,18]. Recent studies have reported the impact of gestational age at delivery on outcomes of neonatal heart surgery [19]. Our data suggests better neurodevelopmental outcomes for infants born at full term compared to early term deliveries [5]. There is a common practice to plan a early (<39 weeks) delivery once a prenatal diagnosis of critical CHD is made to facilitate expedited postnatal cardiac care [20]. Delivery before full term may have a greater impact on brain development and neurodevelopmental outcomes [21,22]. Postnatal studies in term neonates with complex CHD have shown smaller head circumferences compared with normal term neonates [21-23]. Possible reasons attributed to this include cerebral hypo-oxygentation, shared genetic or environmental or placental factors [23]. It is possible that some of these factors may persist despite surgical correction of the CHD, thus influencing neurodevelopmental outcomes. Studies have shown that head circumference at birth is a predictor of head circumference at 1 year of age, thereby explaining our observation of lower head circumference at 1-year follow-up predicting lower PDI [3,24]. Cerebral perfusion pressure, mean cerebral blood flow velocity and regional cerebral oxygen saturation index (rSO2i) would have been better indicators of the adequacy of cerebral blood flow on CPB and in predicting hypoxic ischemic and reperfusion injury [25].

Our results suggest that a pre-operative neurodevelopmental evaluation needs to be done for all patients undergoing surgery for CHD. Neuro-developmental evaluation should be included in the follow-up of all patients, and early intervention program should be initiated whenever deficits are detected. Neurodevelopmental clinics need to function in collaboration with a multidisciplinary team comprising of developmental pediatrician, neurologist, pediatric cardiologist and occupational therapist [26]. Longer follow-up is needed to assess the overall development of these children in higher intellectual domains and executive functions.

In conclusion, psychomotor developmental and mental developmental scores are delayed in 14.5% of infants one year after corrective infant heart surgery and are dynamic in nature. Patient-specific factors like early term birth and lower head circumference at one-year after surgery predicted neurodevelopmental outcomes than cardiac factors.

Contributors: RSS: designed the study, collected and analyzed data and drafted the initial manuscript. TS: did the neurodevelopmental follow up; AS: did the data analysis and revised the manuscript; RKK: contributed to the study design and revised the manuscript; BV: conceptualized and designed the study, analyzed the data, reviewed and edited the manuscript and shall act as the guarantor for the manuscript.
Funding: None; *Competing interests*: None stated.

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WEB TABLE I BASELINE DEMOGRAPHIC AND PERI-OPERATIVE CHARACTERISTICS IN CHILDREN WITH CORRECTIVE CARDIAC SURGERY (*N*=162)

Characteristics	*No. (%)*
Demographic factors	
Age at surgery <1 mo	52 (32.1)
Male gender	92 (56.8)
Socioeconomic status, SE-A	79 (51.3)
Gestational age <39 wk	42 (25.9)
Congenital Heart Diseases	
Ventricular Septal Defect	56 (34.6)
Transposition of Great Arteries	36 (22.2)
Total Anomalous Pulmonary Venous Connection	25 (15.4)
Tetrology of Fallot	21 (12.9)
Anomalous Origin of Left Coronary Artery from Pulmonary Artery	9 (5.6)
Coarctation of Aorta	4 (2.5)
Patent Ductus Arteriosus	3 (1.9)
Others[$]	8 (4.8)
RACHS Category	
1	5 (3.1)
2	91 (56.2)
3	40 (24.7)
4	26 (16.0)
PGE1 infusion	25 (15.4)
Nature of surgery- Emergency	54 (33.3)
Preoperative ventilation (h), *n*=25	32.0 (14.0–74.0)[#]
Preoperative saturation, *n*=162	88.0 (15.07)[*]
Preoperative hematocrit, *n*=162	39.2 (7.97)[*]
CPB time (min), *n*=155	109 (72–196)[#]
ACC time (min), *n*=159	58 (32.0–107)[#]
Minimum hematocrit, *n*=155	28.4 (3.11)[*]
Lowest nasal temperature on CPB (C), *n*=155	29.2 (2.88)[*]
Lowest rectal temperature on CPB (C), *n*=90	28.4 (2.97)[*]
Mean perfusion pressure on CPB (mm Hg), *n*=155	38.4 (4.11)[*]

[*]Mean (SD); [#]Median (IQR); SE- A: Socioeconomic Class I (Upper class) and II (Upper middle); RACHS: Risk Assessment for Congenital Heart Surgery 1; [$]Atrial Septal Defect, Aortopulmonary window, Complete AV canal defect, Interrupted/Hypoplastic arch; CPB: Cardiopulmonary bypass; ACC: Aortic cross clamp.