Neurodevelopmental outcomes in children with cyanotic congenital heart disease following open heart surgery

Samir Shakya[1], Anita Saxena[1], Sheffali Gulati[2], Shyam Sunder Kothari[1], Sivasubramanian Ramakrishnan[1], Saurabh Kumar Gupta[1], Velayoudam Devagourou[3], Sachin Talwar[3], Palleti Rajashekar[3], Shobha Sharma[2]

[1]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India, [2]Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, [3]Department of Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Background : **Neurodevelopmental abnormalities are common in congenital heart disease (CHD), more so in cyanotic CHDs. Perioperative factors have been known to affect neurodevelopmental outcomes.**

Aim : **We aimed to determine the neurodevelopmental outcomes following open-heart surgery in cyanotic CHD.**

Methods : **In this prospective observational study, eligible infants and children ≤21 months with cyanotic CHD planned for open-heart surgery underwent preoperative neurodevelopmental assessment using Developmental Assessment Scale for Indian Infants (DASII) to look for any motor and/or mental delay. A second neurodevelopmental assessment was performed after 9 months ± 2 weeks of cardiac surgery. Follow-up DASII was conducted through interactive video conferencing in 23 of 60 patients due to COVID-19 pandemic. The univentricular and biventricular repair groups were compared in terms of their neurodevelopmental outcomes. Perioperative factors were compared between neurodevelopmental "delay" and "no delay" groups.**

Results : **Of the 89 children enrolled, preoperative motor and mental delay were present in 29 and 24 children, respectively. Follow-up DASII could be performed in 60 children. At follow-up, motor delay was present in seven and mental delay in four children. Overall, there was a significant improvement in both motor and mental developmental quotient at follow-up. There was no significant difference in either motor or mental domains between univentricular and biventricular groups. Among the perioperative variables, only the postoperative length of stay in intensive care unit was significantly different between neurodevelopmental "delay" and "no delay" groups ($P = 0.04$).**

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.apc_149_21

How to cite this article: Shakya S, Saxena A, Gulati S, Kothari SS, Ramakrishnan S, Gupta SK, *et al*. Neurodevelopmental outcomes in children with cyanotic congenital heart disease following open heart surgery. Ann Pediatr Card 2022;15:4-12

Address for correspondence: Dr. Anita Saxena, Department of Cardiology, 7th Floor, Cardiothoracic Sciences Center, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: anitasaxena@hotmail.com

Submitted: 25-Jul-2021 **Revised:** 06-Sep-2021 **Accepted:** 03-Oct-2021 **Published:** 14-Jun-2022

Conclusion : **Neurodevelopmental delay occurred substantially among unoperated children with cyanotic CHD. The neurodevelopmental status improved significantly following open-heart surgery among the survivors. Delay was associated with length of stay in intensive care following cardiac surgery.**

Keywords : Biventricular repair, congenital heart disease, cyanotic, neurodevelopmental outcomes, univentricular repair

INTRODUCTION

The advances in surgical techniques and intensive care have made early surgery of complex congenital heart disease (CHD) possible with low mortality. With improvement in the survival of CHD, the focus which previously was on short-term survival alone has now transitioned to long-term morbidity including neurodevelopmental outcomes.

Neurodevelopmental abnormalities are common among children with complex CHD, including those with cyanotic CHD, affecting approximately half of the survivors as they mature.[1,2] The impairment broadly involves motor and mental domains. The prevalence of neurodevelopmental impairment increases with complexity of the CHD.[3]

Central nervous system (CNS) injury in children with CHD is related to patient-specific factors as well as perioperative care at the time of cardiac surgery. Cerebral ischemia before, during, and after cardiac surgery has been proposed to be the primary mechanism of CNS injury. Children who require cardiac surgery as neonates or young infants have a significantly higher incidence of academic difficulties, behavioral abnormalities, fine and gross motor delays, problems with visual-motor integration and executive planning, speech delays, inattention, and hyperactivity.[4,5] Numerous studies from developed countries indicate a significant proportion of infants and children with CHD have neurodevelopmental delay following surgery on short and mid-term follow-up.[6-10] However, data from developing countries are sparse, where public health awareness as well as availability of expertise for managing CHD are limited.[11,12]

The main objective of the study was to determine the neurodevelopmental outcomes following open-heart surgery in cyanotic CHD. In addition, we aimed to determine the baseline neurodevelopmental status, look for differences in neurodevelopmental outcomes between univentricular and biventricular repair groups and identify perioperative factors predicting the neurodevelopmental outcomes.

METHODS

Study design

In this single-center prospective observational study, infants and children ≤21 months of age with cyanotic CHD who were planned for open-heart surgery were recruited from pediatric cardiology and cardiothoracic surgery wards. The study was approved by the Institutional Ethics Committee and was conducted between June 2018 and July 2020. Informed consent was taken from patient's legally authorized representative. Patients were excluded if they had undergone open-heart surgery previously or had neurological abnormalities present preoperatively (except developmental abnormalities) or were too sick to preclude neurodevelopmental assessment by Developmental Assessment Scale for Indian Infants (DASII). Preterm babies and those with clinically recognizable chromosomal abnormalities or syndromes with neurodevelopmental disabilities were also excluded.

DASII is used for neurodevelopmental assessment in children.[13,14] DASII is a revision of the Baroda development screening test for infants which is based on the Bayley Scale of Infant Development and is validated for Indian children between 0 and 30 months. Motor developmental quotient (DQ) and mental DQ can be calculated by this scale. A DQ score of more than 85 is considered as normal.[15] Developmental delay is defined as DQ ≤70 (≤ −2SD) in either the mental or motor scale. The age cut-off of 21 months was chosen in this study as DASII is validated only for children up to 30 months, and the follow-up assessment was planned at 9 months ± 2 weeks.

The preoperative details of the patient such as age, weight, oxygen saturation, cardiac diagnosis, preoperative percutaneous intervention, preoperative length of hospital and intensive care unit (ICU) stays, and preoperative mechanical ventilation (if required) were noted. Weight for age Z-scores was calculated using Anthro version 3.2.2 (WHO, Geneva, Switzerland), a software developed by the World Health Organization (WHO) for monitoring growth in children of 0–60 months. Preoperative risk score based on the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) classification was calculated for the study population.[16] Neurodevelopmental assessment was carried out using DASII preoperatively by a trained clinical psychologist in the Child Neurology division, Department of Pediatrics within 7 days before surgery. Following surgery, the operative details were collected and patients were followed up during the postoperative period. The intraoperative variables noted were type

of surgical procedure, durations of cardiopulmonary bypass (CPB) and aortic cross-clamp time, duration of deep hypothermic circulatory arrest (if used), lowest temperature during CPB, and lowest hematocrit on CPB. Postoperative variables that were noted include lengths of ICU and hospital stay postoperatively, durations of mechanical ventilation and inotropic support, need of extracorporeal membrane oxygenation (ECMO) support, need for re-exploration, occurrence and duration of hypotension, occurrence of hypoglycemia, or other complications such as seizures and cardiac arrest. A postoperative echocardiogram was performed in all patients, and the presence of residual or new lesions was noted. Predischarge oxygen saturation of the patients was also recorded.

Neurodevelopmental assessment using DASII was repeated at 9 months ± 2 weeks following cardiac surgery. The clinical psychologist performing the neurodevelopmental assessments was blinded to the diagnosis and operative details of the patients.

In view of the COVID-19 pandemic, the follow-up DASII assessment of patients in later part of the study was done through interactive video conferencing. Ethical approval for conducting DASII by video conferencing was taken. The items in the motor and mental domains that the child could perform as per DASII format were noted using the child's own toys and household objects as tools for assessment.

Statistical analysis

All analyses were performed using IBM SPSS Statistics software for Windows, version 23 (IBM Corp., Armonk, NY, USA). All continuous variables were expressed as mean ± standard deviation for parametric data and median (minimum– maximum) for nonparametric data. All categorical variables were expressed as frequency (%). The comparison of each continuous variable between univentricular and biventricular groups was done using Wilcoxon rank-sum test. The comparison of each categorical variable between univentricular and biventricular groups was done using Fisher's exact test. The comparison of parameters before surgery and at follow-up (e.g., oxygen saturation, mean DQ) was done using Paired *t*-test. The motor and mental DQ obtained at follow-up by in-person DASII and by video-conferencing were compared by Independent samples *t*-test. The comparison of each perioperative factor between the "delay" group (DQ ≤70) and "no delay" group (DQ >70) was done using Wilcoxon rank-sum test and Fisher's exact test.

RESULTS

Baseline characteristics

During the study period, 89 children were enrolled in the study. However, postoperative follow-up assessment could be done in 60 cases only. Remaining patients either expired in hospital (18) or after discharge due to respiratory infections before the assessment could be done (9) or lost to follow-up (2).

Seventy-seven (86.5%) patients were infants under 1 year of age. Seventy eight (88%) had weight for age Z-score <-2. D-transposition of great arteries (TGA) with intact ventricular septum was the most common diagnosis (29.2%), followed by D-TGA with ventricular septal defect (VSD) (25.8%) and total anomalous pulmonary venous connection (TAPVC, 16.9%) [Table 1]. The median duration of preoperative hospital stay was 10 days (range: 1–43 days). Seventy (79%) patients required preoperative ICU stay. The patients who had a longer duration of hospital stay preoperatively required medical stabilization for severe desaturation (prostaglandin E1 infusion, balloon atrial septostomy [BAS]), treatment of probable sepsis and lower respiratory tract infection, and hemodynamic stabilization for heart failure and shock. Preoperative BAS was required in 33 (37%) patients, all of whom had diagnosis of D-TGA except two, who had diagnosis of cardiac TAPVC with restrictive atrial septal defect. Preoperative mechanical ventilation was required for apnea (in those requiring prostaglandin E1 infusion), severe lower respiratory tract infection, heart failure and shock. Five out of 19 patients who required preoperative mechanical ventilation expired postoperatively before hospital discharge. The baseline preoperative details of the patients have been presented in Table 2.

Table 1: Preoperative diagnosis of patients and types of surgery

Preoperative diagnosis	Frequency, *n* (%)	Type of surgery
D-TGA, IVS	26 (29.2)	All biventricular
D-TGA, VSD	23 (25.8)	All biventricular
D-TGA, VSD, LVOTO	4 (4.5)	All biventricular
TAPVC	15 (16.9)	All biventricular
TOF and TOF variants	10 (11.2)	All biventricular, except 1 with only TAP
Tricuspid atresia	3 (3.4)	All univentricular
Truncus arteriosus*	2 (2.2)	All biventricular
Taussig-Bing anomaly#	2 (2.2)	All biventricular
DORV, VSD, severe PS	1 (1.1)	Biventricular
DORV, MPGA (single ventricle physiology)	1 (1.1)	Univentricular
AVSD, Severe PS (single ventricle physiology)	2 (2.2)	Univentricular
Total	89 (100)	

*1 patient had associated interrupted aortic arch and had undergone arch repair in addition, #1 patient had congenital complete heart block also and required epicardial pacemaker implantation along with the complete repair. AVSD: Atrioventricular septal defect, DORV: Double outlet right ventricle, IVS: Intact ventricular septum, LVOTO: Left ventricular outflow tract obstruction, MPGA: Malposed great arteries, PS: Pulmonary stenosis, TAPVC: Total anomalous pulmonary venous connection, TAP: Transannular patch, TOF: Tetralogy of Fallot, TGA: Transposition of great arteries, VSD: Ventricular septal defect

The patients were divided into univentricular and biventricular groups based on the type of surgery they underwent. Eighty-three patients underwent biventricular repair and 6 underwent univentricular repair (Glenn shunt). One patient in biventricular group underwent only transannular patch (TAP) leaving VSD open due to small branch pulmonary arteries.

Intraoperative details

The most common surgery in the biventricular repair group was arterial switch operation (ASO), while all patients in univentricular repair group had a bidirectional Glenn shunt [Figure 1]. The details of intraoperative parameters for the sixty patients with follow-up data have been presented in Table 3. Majority of the patients fell in RACHS-1 category 3 (37.1%) followed by RACHS-1 category 4 (36%). The overall predicted mortality rate from the RACHS-1 model would be 11.2%.

Postoperative details

The durations of postoperative ICU stay, mechanical ventilation, and inotropic support were significantly longer in the biventricular group compared to the univentricular group. Among 12 patients requiring postoperative ECMO, there were 3 survivors, all were in biventricular group diagnosed as D-TGA with intact ventricular septum. Among all the operated patients (89), 15 (16.8%) patients had sepsis, two of whom were culture positive. There were rhythm disturbances such as complete heart block in two-requiring permanent epicardial pacemaker implantation, sinus node dysfunction, junctional ectopic tachycardia, and

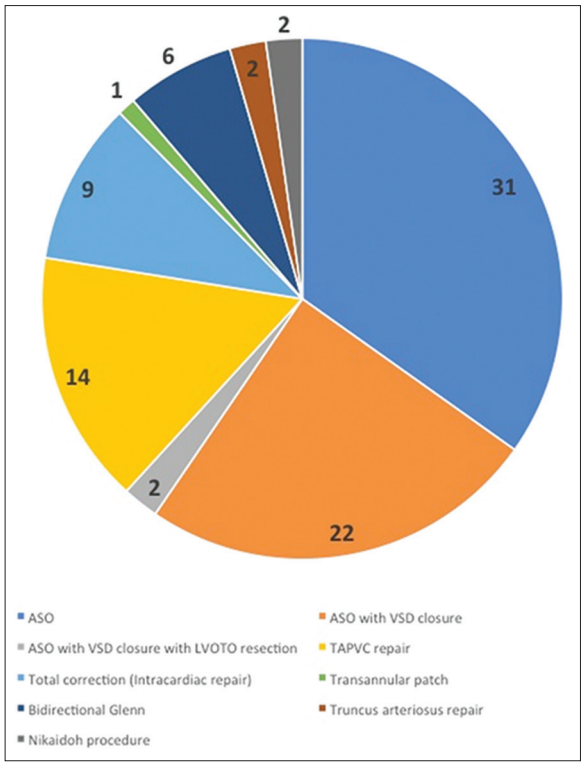

Figure 1: Pie chart showing types of cardiac surgeries performed (total patients = 89). ASO: Arterial switch operation, LVOTO: Left ventricular outflow tract obstruction, TAPVC: Total anomalous pulmonary venous connection, VSD: Ventricular septal defect

Table 2: Preoperative patient characteristics

Variables	Overall (*n*=89)*	Median (minimum–maximum)		*P*
		Biventricular (*n*=83)	Univentricular (*n*=6)	
Age (months)	3 (0.33-21)[a]	3 (0.33-21)	10.5 (4-18)	0.008
Weight (kg)	4.42 (1.88)[b]	3.5 (2.3-10)	7.35 (3.7-8)	0.006
Male gender, *n* (%)	66 (74.2)	63 (75.9)	3 (50)	0.16
Preoperative SpO2	73.62 (7.89)[b]	75 (40-86)	71 (60-75)	0.063
Preoperative length of hospital stay	10 (1-43)[a]	12 (1-43)	2 (1-3)	0.001
Preoperative BAS, *n* (%)	33 (37.1)	33 (39.8)	0	-
Preoperative mechanical ventilation, *n* (%)	19 (21.3)	19 (22.9)	0	-

[a]Median (minimum–maximum), [b]Mean±SD. BAS: Balloon atrial septostomy, Spo2: Arterial oxygen saturation, SD: Standard deviation

Table 3: Data on intraoperative variables (for 60 patients with follow-up)

Variables	Overall (*n*=60)*	Median (minimum–maximum)		*P*
		Biventricular (*n*=56)	Univentricular (*n*=4)	
CPB time (min)	158.5 (22-330)[a]	163.5 (22-330)	47.5 (43–74)	0.001
AoXCl time (min)	86 (0-240)[a]	91 (12-240)	7 (0–29)	0.000
Lowest temperature on CPB (°C)	28.81 (2.05)[b]	28 (26-36)	32 (31–36)	0.001
Minimum hematocrit on CPB	33.5 (3.78)[b]	33.5 (25-40)	35 (33–38)	0.320
Use of DHCA, n (%)	0	0	0	-
RACHS - 1 categories		**Mortality, *n* (%)**		
Category 1		-		
Category 2		2 (8.7)		
Category 3		6 (18.2)		
Category 4		9 (28.1)		
Category 5		1 (100)		

[a]Median (minimum–maximum), [b]Mean±SD. AoXCl: Aortic cross-clamp, CPB: Cardiopulmonary bypass, DHCA: Deep hypothermic circulatory arrest, RACHS-1: Risk adjustment for congenital heart surgery-1

supraventricular tachycardia. Among 19 patients who required cardiopulmonary resuscitation (CPR), only one was revived following a brief CPR for 2 min and later discharged. The details of postoperative course for the surviving sixty patients with follow-up data are provided in Table 4. The mean postoperative oxygen saturation on discharge was 96.9% in the biventricular group and 82.5% in the univentricular group. Overall, there was a significant improvement in oxygen saturation at the time of discharge [Table 5].

Neurodevelopmental assessment

Preoperative

Out of the 89 patients, 69 had to be medically stabilized before preoperative neurodevelopmental assessment could be performed. All underwent cardiac surgery within 7 days of assessment by DASII. Overall preoperative motor and mental delay were found in 29 (35.4%) and 24 (29.3%) patients, respectively. Both preoperative motor and mental delay were present in 21 (23.6%) patients. The mean motor DQ in the biventricular group (n = 83) was 75.96 ± 19.28 and that in the univentricular group (n = 6) was 71 ± 17.46. The mean mental DQ in the biventricular group was 78.94 ± 16.51 and that in the univentricular group was 70.67 ± 15.51. There was no significant difference in the baseline motor and mental DQ between two groups (P values of 0.43 and 0.25, respectively).

On postoperative follow-up

The neurodevelopmental assessment at follow-up was done in 60 patients, at interval of 9.15 ± 0.29 months. Mean age at follow-up was 14.8 ± 5.7 months overall, 20.7 ± 6.1 months for univentricular group and 14.4 ± 5.5 months for biventricular group. Out of the 60 patients followed up, the follow-up DASII assessment was done via video conferencing in 23 (38.3%) patients due to the COVID-19 pandemic. The follow-up motor and mental DQ are depicted in Table 5. There was no significant difference in the DQ scores obtained by in-person assessment and by video conferencing [Table 6].

The mean follow-up motor DQ and mental DQ overall were 83.74 ± 12.58 and 85.63 ± 10.83, respectively. Overall, both motor and mental DQ improved significantly at follow-up (P value of 0.012 and 0.019, respectively). However, the improvement was significant in biventricular group (P value of 0.010 for motor DQ and 0.043 for mental DQ) but not in univentricular group. The changes from preoperative to follow-up DQ for biventricular and univentricular groups are shown in Figure 2. On comparing the DQ obtained by in-person assessment and by video conferencing, there was no significant difference between the two modes of assessment.

Patients with motor delay on follow-up

Seven patients had motor delay on follow-up. Out of them, three had isolated motor delay while 4 had both motor and mental delay (described below). Among those with isolated motor delay, two had undergone bidirectional Glenn while one had undergone ASO with VSD closure. Only one of the three had preoperative motor delay.

Patients with mental delay on follow-up

Four patients had mental delay, two of these had this delay preoperatively also. One had undergone TAP alone initially and off-pump emergency modified Blalock-Taussig shunt for refractory spell, 5 months before follow-up assessment. Two had undergone preoperative BAS, with one baby having septic shock preoperatively requiring mechanical ventilation and prolonged hospital stay preoperatively. The fourth patient with mental delay had severe preoperative hypoxia and delayed motor as well as mental development preoperatively. In addition, he required long CPB and aortic cross-clamp times (294 and 205 min, respectively).

Table 4: Data on postoperative variables (for 60 patients with follow-up)

Variables	Overall (n=60)	Median (minimum–maximum)		P
		Biventricular (n=56)	Univentricular (n=4)	
Length of ICU stay (days)	7.5 (1-48)[a]	8 (1-48)	4.5 (2-7)	0.046
Length of hospital stay (days)	12.5 (5-56)[a]	13 (5-56)	6 (5-17)	0.058
Duration of mechanical ventilation (days)	3 (0.23-31)[a]	3 (0.25-31)	0.29 (0.23-1)	0.001
Duration of inotropic support (h)	125 (15-900)[a]	140 (30-900)	45 (15-136)	0.002
Need of ECMO support, *n* (%)	3 (5)	3 (5.4)	0	-
Duration of ECMO support (days)	3.33 (1.16)[b]	4 (2-4)	0	-
Persistent hypotension, *n* (%)	17 (28.3)	17 (30.4)	0	-
Duration of hypotension (h)	6 (2-72)[a]	6 (2-72)	0	-
Hypoglycemia, *n* (%)	1 (1.7)	1 (1.8)	0	-
Seizures, *n* (%)	1 (1.7)	1 (1.8)	0	-
Cardiac arrest, *n* (%)	1 (1.7)	1 (1.8)	0	-
Focal deficit, *n* (%)	0	0	0	-
Re-intervention, *n* (%)	2 (3.3)	2 (3.6)	0	-
Residual defect on echocardiography, *n* (%)	9 (15)	9 (16.1)	0	-
Postoperative saturation on discharge	95.9 (4.9)[b]	97 (74-100)	81.5 (76-87)	0.000

[a]Median (minimum–maximum), [b]Mean±SD. ECMO: Extracorporeal membrane oxygenation, ICU: Intensive care unit

Table 5: Comparison of developmental quotients and oxygen saturations before surgery and at follow-up

Variables	Preoperative (total=60)	Postoperative or follow-up (total=60)	*P*
Motor DQ (n=60), mean±SD	77.25±16.77	83.74±12.57	0.012
Univentricular (*n*=4)	72.5 (18.12)	74.83 (21.44)	0.88
Biventricular (*n*=56)	77.59 (16.79)	84.38 (11.77)	0.010
Mental DQ (*n*=60), mean±SD	80.62±13.94	85.63±10.83	0.019
Univentricular (*n*=4)	72.25 (19.05)	86.50 (11.27)	0.25
Biventricular (*n*=56)	81.21 (13.54)	85.57 (10.90)	0.043
Oxygen saturation (*n*=60), mean±SD	73.9±6.9	95.9±4.9	0.000
Univentricular (*n*=4)	70.2 (5.9)	82.5 (3.1)	0.013
Biventricular (*n*=56)	74.2 (6.9)	96.9 (3.3)	0.000

DQ: Developmental quotient, SD: Standard deviation

Table 6: Comparison of follow-up developmental quotient obtained by in-person assessment and by video conferencing

	Follow-up motor DQ*	*P*	Follow-up mental DQ*	*P*
In-person DQ (*n*=37)	81.24 (10.76)	0.05	84.19 (8.77)	0.19
Video conferencing DQ (*n*=23)	87.76 (14.39)		87.96 (13.41)	

*Values presented as means±SD. DQ: Developmental quotient, SD: Standard deviation

Association of motor and mental development with perioperative parameters has been shown in Tables 7 and 8, respectively. The duration of postoperative ICU stay was found to be significantly longer in those with delayed mental development ($P = 0.04$), but not for delay in motor development. Other perioperative variables, including the use of ECMO, were not significantly associated with motor or mental delay. Regression analysis could not be performed to check the effect of individual perioperative variables on the final motor and mental DQ because the number of patients with motor and mental delays at follow-up was small.

DISCUSSION

Preoperative neurodevelopmental status

Using DASII, preoperative motor delay was found in 35.4% of children while preoperative mental delay was found in 29.3% of children and 23.6% had both types of delay. In a preoperative cohort of children with CHD aged 6–30 months studied by Lata *et al.*, motor delay was found in 48% and mental delay in 12% of children.[17] The motor DQ has been reported to be in the abnormal range in infants during the recovery stage of their acute sickness.[18] However, in the current study, all patients underwent preoperative neurodevelopmental assessment when medically stable.

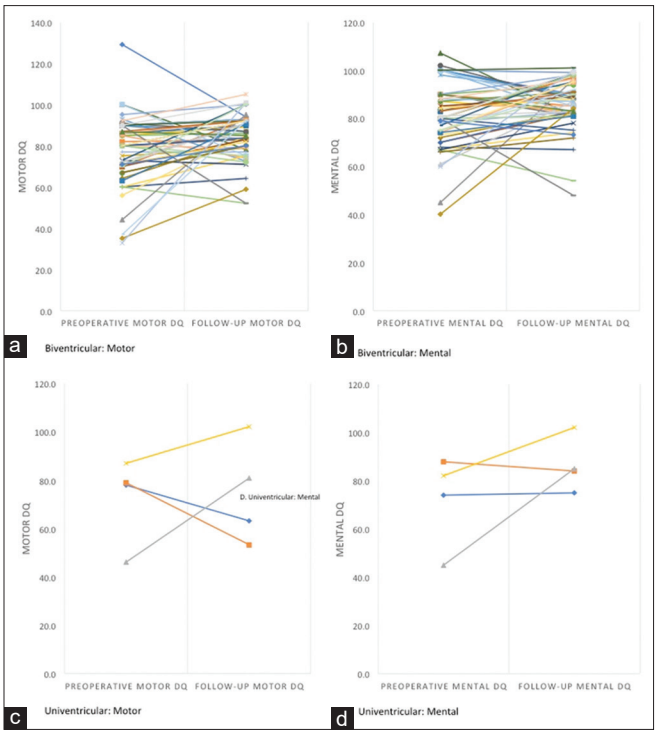

Figure 2: Line diagram showing preoperative and follow-up DQ scores (total patients = 60). DQ: Developmental quotient

Neurodevelopmental status at follow-up

A significant improvement in both mean motor and mean mental DQ scores was observed at follow-up. The improvement in motor as well as mental DQ was statistically significant in biventricular group while the improvement in univentricular group was not statistically significant. The pattern of neurodevelopmental delay observed in our study is similar to that in other studies, with motor domain affected more than mental domain.[10,19,20]

The proportion of children having neurodevelopmental delay at short-term follow-up seems to be much less as compared to other studies which have looked into the neurodevelopmental outcomes following open heart surgery.[6,7,9,20] It is noteworthy that none of these studies included cyanotic CHDs alone. One reason for the lower neurodevelopmental delay observed at follow-up may be related to a high surgical mortality (20.2%) which would have filtered out the poorer subset who had done worse preoperatively as well as postoperatively. Moreover, nine patients had expired following discharge from hospital till their stipulated time of follow-up. The other reason for good DQ scores at follow-up may be the significant improvement in oxygen saturation at hospital discharge in these cyanotic children. Limperopoulos *et al.* had demonstrated that persisting cyanosis at follow-up was associated with gross motor delay.[7] Our study suggests that on the improvement of hypoxia, the neurodevelopmental status also improves.

Table 7: Perioperative factors and motor development at follow-up

Variables	Median (minimum–maximum)		*P*
	Motor DQ ≤70 (*n*=7)	Motor DQ >70 (*n*=53)	
Age (months)	8 (1.5-20)	3 (0.33-21)	0.19
Weight (kg)	4.1 (3-8.2)	3.4 (2.3-10)	0.16
Gender, *n* (%)			
Male	3 (6.9)	40 (93.1)	0.092
Female	4 (23.5)	13 (76.5)	
Preoperative spO2	72 (52-77)	75 (60-86)	0.085
Preoperative BAS, *n* (%)			
Yes	1 (4.5)	21 (95.5)	0.25
No	6 (15.8)	32 (84.2)	
Preoperative LOS (days)	3 (1-39)	10 (1-43)	0.31
Preoperative ventilation (days), *n* (%)			
Yes	1 (9.1)	10 (90.9)	0.99
No	6 (12.2)	43 (87.8)	
CPB time (min)	139 (22-294)	163 (40-330)	0.47
AoXCl time (min)	55 (0-205)	89 (14-240)	0.19
Minimum temperature (°C)	28 (28-36)	28 (26-34)	0.05
Hematocrit	35 (32-40)	33 (25-40)	0.19
ICU stay (days)	12 (2-48)	7 (1-43)	0.40
Hospital stay (days)	15 (5-56)	12 (5-48)	0.25
Mechanical ventilation (days)	2 (0.23-28)	3 (0.25-31)	0.62
Persistent hypotension, *n* (%)			
Yes	0	17 (100)	0.17
No	7 (16.3)	36 (83.7)	
Inotrope duration (h)	216 (15-390)	120 (30-900)	0.29
Need for ECMO, *n* (%)			
Yes	0	3 (100)	0.99
No	7 (12.3)	50 (87.7)	
Need for cardiac reintervention, *n* (%)			
Yes	0	2 (100)	0.99
No	7 (12.1)	51 (87.9)	
Residual lesion, *n* (%)			
Yes	1 (11.1)	8 (88.9)	0.99
No	4 (8.5)	43 (91.5)	
Postoperative Spo2 at discharge	96 (74-99)	97 (80-100)	0.38

AoXCl: Aortic cross-clamp, BAS: Balloon atrial septostomy, CPB: Cardiopulmonary bypass, ECMO: Extracorporeal membrane oxygenation, ICU: Intensive care unit, LOS: Length of stay, Spo2: Oxygen saturation, DQ: Developmental quotient

Dittrich *et al*. and Sananes *et al*. found poor motor development following palliative surgeries,[9,21] while Mussatto *et al*. found equivalent neurodevelopmental outcomes in single ventricle and biventricular groups.[8] In our study, no significant difference was observed between the two groups possibly because of small numbers in univentricular group.

Role of perioperative factors

The patient-related factors have been incriminated as predictors of neurodevelopmental outcomes after open-heart surgery in children.[10,19,22] In our study, no significant difference in terms of the preoperative variables was found between the delay group and no delay group (for both motor and mental domains) at follow-up. A longer duration of CPB has been associated with poor neurodevelopmental outcomes in previous studies.[8,23] However, the durations of CPB and aortic cross-clamp did not show significant difference between the delay and no delay groups in our study.

A long duration of postoperative ICU and hospital stay has been reported to be associated with adverse neurodevelopmental outcomes by several authors.[7,21,23-25] In our study also, a significant difference in the duration of postoperative ICU stay was observed between the mental delay and no mental delay groups at follow-up.

Hamrick *et al*. found the use of ECMO was associated with lower developmental indices.[26] Our study had only three patients who survived following ECMO support, all three revealed no motor or mental delay. Kabbani *et al*. found poor neurodevelopmental outcomes in children who suffered postoperative cardiac arrest and this was related to the duration of CPR and number of cardiac arrest events.[27] In our study, the single survivor of postoperative cardiac arrest didn't have motor or mental delay at follow-up.

The in-hospital mortality of patients undergoing open-heart surgery was 20.2%. However, the predicted mortality from RACHS-1 classification was 11.2%. This high mortality can be attributed to the preoperative sickness status of some patients. A significant number of patients had high level of sickness preoperatively, such as sepsis, requirement for mechanical ventilation, catheter intervention, and need for preoperative ICU stay. Requirement of preoperative intensive care and mechanical ventilation have been associated with adverse postoperative outcomes in infant heart surgery.[28,29] Murni *et al*. reported a 30-day mortality of 13.6% in their cohort of children undergoing congenital heart surgery. Cyanotic CHD was associated with major complications and mortality after cardiac surgery in their study.[30] All the patients in our study had cyanotic CHD. Moreover, majority of the study population had poor preoperative nutritional status as suggested by weight for age Z score <-2. A significant association between preoperative malnutrition and 30-day mortality after pediatric cardiac surgery has been demonstrated by Ross *et al*.[31] Similarly, the most common diagnosis in our study was D-TGA, including those with intact ventricular septum and VSD. A significant number of patients needing ECMO and high mortality postoperatively can be the result of high proportion of late presenting D-TGA, especially those with intact ventricular septum. In addition, impaired brain growth and delayed neurodevelopment have been found in infants with D-TGA undergoing ASO beyond 2 weeks of age.[32] In our study, four of thirty-five patients of D-TGA who were followed had neurodevelopmental delay.

Table 8: Perioperative factors and mental development at follow-up

Variables	Median (minimum–maximum)		*P*
	Mental DQ ≤ 70 (*n*=4)	Mental DQ>70 (*n*=56)	
Age (months)	2.5 (1.5-20)	3 (0.33-21)	0.90
Weight (kg)	3.4 (3-8.2)	3.4 (2.3-10)	0.79
Gender, *n* (%)			
Male	2 (4.6)	41 (93.4)	0.32
Female	2 (11.8)	15 (88.2)	
Preoperative spO2	65.5 (52-77)	75 (60-86)	0.06
Preoperative BAS, *n* (%)			
Yes	1 (4.6)	21 (95.4)	0.99
No	3 (7.9)	35 (92.1)	
Preoperative LOS (days)	9 (1-39)	10 (1-43)	0.74
Preoperative ventilation (days), *n* (%)			
Yes	1 (9.1)	10 (90.9)	0.57
No	3 (6.1)	46 (93.9)	
CPB time (min)	145.5 (22-294)	163 (40-330)	0.84
AoXCl time (min)	62 (12-205)	88 (0-240)	0.49
Minimum temperature (°C)	28 (28-36)	28 (26-36)	0.54
Hematocrit	35 (34-40)	33 (25-40)	0.15
ICU stay (days)	12 (12-48)	7 (1-43)	0.04
Hospital stay (days)	18.5 (13-56)	12 (5-48)	0.06
Mechanical ventilation (days)	3.5 (2-28)	3 (0.23-31)	0.57
Persistent hypotension, *n* (%)			
Yes	0	17 (100)	0.57
No	4 (9.3)	39 (90.7)	
Inotrope duration (h)	228 (144-276)	120 (15-900)	0.059
Need for ECMO, *n* (%)			
Yes	0	3 (100)	0.99
No	4 (7)	53 (93)	
Need for cardiac reintervention, *n* (%)			
Yes	0	2 (100)	0.99
No	4 (6.9)	54 (93.1)	
Residual lesion, *n* (%)			
Yes	0	9 (100)	0.99
No	4 (8.5)	43 (91.5)	
Postoperative Spo2 at discharge	98.5 (74-99)	97 (80-100)	0.36

AoXCl: Aortic cross-clamp, BAS: Balloon atrial septostomy, CPB: Cardiopulmonary bypass, ECMO: Extracorporeal membrane oxygenation, ICU: Intensive care unit, LOS: Length of stay, Spo2: Oxygen saturation, DQ: Developmental quotient

Limitations of the study

Due to the COVID-19 pandemic, the follow-up DASII was performed via video conferencing in 23 (38.3%) patients. Although a good agreement has been shown in the literature between in-person and video conference-based neurodevelopmental assessment,[33,34] the two methods of assessment are different. The number of patients in the univentricular group was substantially less as compared to the biventricular group. The comparison between two groups with substantially different numbers may not be accurate. The number of patients with motor as well as mental delay at follow-up was low. Thus, the effects of perioperative factors on final neurodevelopmental outcomes could not be assessed. Hence, only the difference between "delay" and "no delay" groups in terms of various perioperative variables have been mentioned. The strength of the study is that both preoperative (baseline) and follow-up DQ have been assessed, making it possible to objectively gauge the effect of surgery and postoperative factors on neurodevelopment.

CONCLUSIONS

Neurodevelopmental delay occurred substantially among unoperated children with cyanotic CHD. Following open-heart surgery, neurodevelopmental status in terms of motor and mental DQ improved significantly among those who were followed up at 9 months following cardiac surgery. Thus, we conclude that neurodevelopmental status improves reasonably at short-term follow-up among the survivors of open-heart surgery for cyanotic CHD. Neurodevelopmental delay was associated with longer length of stay in intensive care following cardiac surgery. Further research is warranted to look into the effect of perioperative factors on neurodevelopmental outcomes in cyanotic CHD.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wernovsky G, Licht DJ. Neurodevelopmental outcomes in children with congenital heart disease – What can we impact? Pediatr Crit Care Med 2016;17:S232-42.
2. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status of newborns with congenital heart defects before open heart surgery. Pediatrics 1999;103:402-8.
3. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, *et al.* Neurodevelopmental outcomes in children with congenital heart disease: Evaluation and management: A scientific statement from the American Heart Association. Circulation 2012;126:1143-72.
4. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young 2006;16 Suppl 1:92-104.
5. Wray J, Sensky T. Congenital heart disease and cardiac surgery in childhood: Effects on cognitive function and academic ability. Heart 2001;85:687-91.
6. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, *et al.* Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics 2015;135:816-25.
7. Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C, *et al.* Predictors of

developmental disabilities after open heart surgery in young children with congenital heart defects. J Pediatr 2002;141:51-8.

8. Mussatto KA, Hoffmann RG, Hoffman GM, Tweddell JS, Bear L, Cao Y, *et al.* Risk and prevalence of developmental delay in young children with congenital heart disease. Pediatrics 2014;133:e570-7.
9. Dittrich H, Bührer C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. Heart 2003;89:436-41.
10. Fuller S, Nord AS, Gerdes M, Wernovsky G, Jarvik GP, Bernbaum J, *et al.* Predictors of impaired neurodevelopmental outcomes at one year of age after infant cardiac surgery. Eur J Cardiothorac Surg 2009;36:40-8.
11. Kothari SS. Future of pediatric cardiac care in India. Ann Pediatr Cardiol 2014;7:3.
12. Saxena A. Pediatric cardiac care in India: Current status and the way forward. Future Cardiol 2018;14:1-4.
13. Phatak P, Dhapre M, Pandit AN, Kulkarni S. A study of Baroda development screening test for infants. Indian Pediatr 1991;28:843-9.
14. Phatak P. Manual for using Development Assessment Scales for Indian Infants (DASII): Based on revised Baroda norms. Pune: Anand Agencies; 1997.
15. Juneja M, Mohanty M, Jain R, Ramji S. Ages and stages questionnaire as a screening tool for developmental delay in Indian children. Indian Pediatr 2012;49:457-61.
16. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002;123:110-8.
17. Lata K, Mishra D, Mehta V, Juneja M. Neurodevelopmental status of children aged 6-30 months with congenital heart disease. Indian Pediatr 2015;52:957-60.
18. Yang CF, Xue Y, Feng JY, Jia FY, Zhang Y, Li YM. Gross motor developmental dysfunctional outcomes in infantile and toddler pediatric intensive care unit survivors. BMC Pediatr 2019;19:508.
19. Gaynor JW, Wernovsky G, Jarvik GP, Bernbaum J, Gerdes M, Zackai E, *et al.* Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg 2007;133:1344-53.
20. Solomon RS, Sasi T, Sudhakar A, Kumar RK, Vaidyanathan B. Early neurodevelopmental outcomes after corrective cardiac surgery in infants. Indian Pediatr 2018;55:400-4.
21. Sananes R, Manlhiot C, Kelly E, Hornberger LK, Williams WG, MacGregor D, *et al.* Neurodevelopmental outcomes after open heart operations before 3 months of age. Ann Thorac Surg 2012;93:1577-83.
22. Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M, *et al.* Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: The single ventricle reconstruction trial. Circulation 2012;125:2081-91.
23. International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. Ann Thorac Surg 2016;102:843-9.
24. Newburger JW, Wypij D, Bellinger DC, du Plessis AJ, Kuban KC, Rappaport LA, *et al.* Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. J Pediatr 2003;143:67-73.
25. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental outcome after congenital heart surgery: Results from an institutional registry. Circulation 2002;106:I95-102.
26. Hamrick SE, Gremmels DB, Keet CA, Leonard CH, Connell JK, Hawgood S, *et al.* Neurodevelopmental outcome of infants supported with extracorporeal membrane oxygenation after cardiac surgery. Pediatrics 2003;111:e671-5.
27. Kabbani MS, Alsumih NA, Alsadun SA, Hamadah HK. Five-year survival, performance, and neurodevelopmental outcome following cardiopulmonary resuscitation after pediatric cardiac surgery, preliminary investigation in a single-center experience. J Saudi Heart Assoc 2019;31:161-9.
28. Reddy NS, Kappanayil M, Balachandran R, Jenkins KJ, Sudhakar A, Sunil GS, *et al.* Preoperative determinants of outcomes of infant heart surgery in a limited-resource setting. Semin Thorac Cardiovasc Surg 2015;27:331-8.
29. Simsic JM, Kanter KR, Kirshbom PM, Cuadrado A. Does preoperative mechanical ventilation affect outcomes in neonates undergoing cardiac surgery? Cardiol Young 2007;17:90-4.
30. Murni IK, Djer MM, Yanuarso PB, Putra ST, Advani N, Rachmat J, *et al.* Outcome of pediatric cardiac surgery and predictors of major complication in a developing country. Ann Pediatr Cardiol 2019;12:38-44.
31. Ross F, Latham G, Joffe D, Richards M, Geiduschek J, Eisses M, *et al.* Preoperative malnutrition is associated with increased mortality and adverse outcomes after paediatric cardiac surgery. Cardiol Young 2017;27:1716-25.
32. Lim JM, Porayette P, Marini D, Chau V, Au-Young SH, Saini A, *et al.* Associations between age at arterial switch operation, brain growth, and development in infants with transposition of the great arteries. Circulation 2019;139:2728-38.
33. Brearly TW, Shura RD, Martindale SL, Lazowski RA, Luxton DD, Shenal BV, *et al.* Neuropsychological test administration by videoconference: A systematic review and meta-analysis. Neuropsychol Rev 2017;27:174-86.
34. Dahiya A, McDonnell C, DeLucia E, Scarpa A. A systematic review of remote telehealth assessments for early signs of autism spectrum disorder: Video and mobile applications. Pract Innov 2020;5:150-64.