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PROJECT COMPLETION REPORT

1.	**Project Number**	:	5367
2.	**Title of the Project**	:	Evaluation of intermediate term cardiac and neurodevelopmental outcomes of children undergoing corrective arterial switch operation for complete transposition of great arteries
3.	**Funding Agency Name**	:	National Health Mission
4.	**Project Reference Number provided by the Funding Agency**:		
	NHM/674/JC/(RBSK)/2017/SPMSU		
5.	**Principal Investigator (Name & Address) :**		
	Dr Baiju S Dharan, Professor, CVTS, SCTIMST		
6.	**Co-Principal Investigators (Name & Address):**		
	i. Dr Arun Gopalakrishnan	Department of Cardiology, SCTIMST	
	ii. Dr Sowmya Ramanan	Department of CVTS, SCTIMST	
	iii. Dr Soumya Sundaram	Department of Neurology, SCTIMST	
6b	**Co Investigators (Name & Address):**		
	i. Dr Ajitkumar VK	Department of Cardiology, SCTIMST	
	ii. Dr Jayakumar K	Department of CVTS, SCTIMST	
7.	**Implementing Institution**	:	SCTIMST
8.	**Collaborating Institutions**	:	NA
9.	**Date of Commencement**	:	01/10/2018

10.	**Duration**	:	1 year
11.	**Date of Completion**	:	31/12/2019

12. Objectives as approved :

A cross-sectional study of children who have undergone corrective arterial switch operation under cardiopulmonary bypass in infancy for complete Transposition of great vessels between 2014 and 2015 at SCTIMST for evaluation for their cardiovascular and neuro-developmental outcomes based on routine examination and questionnaire based interaction.

13. Deviation made from original objectives if any, while implementing the project and reasons thereof :

Nil

14. Field/Experimental work giving full details of summary of methods adopted, data collected supported by necessary tables, charts, diagrams and photographs :

All consecutive children who underwent ASO during the study period were included in this retrospective cohort study. Institutional ethics committee clearance (SCT/IEC/1195/AUGUST-2018 dated 06-09-2018) and written informed parental consent in vernacular was obtained for the study. These children were followed up at 3-5 years of age for the assessment of cardiac and neurodevelopmental status.

With a reported 20% incidence of neurodevelopmental delay in ASO survivors in childhood, and a prevalence of 1.4 – 2.4% in young Indian children, we estimated a minimum sample size of 44 for the study cohort against a power of 0.8 and an alpha error of 0.05.

A dedicated unit for evaluation of the children was created using a team approach combining the efforts of the pediatric cardiac surgeons, pediatric cardiologists, pediatric neurologist, clinical psychologist, speech therapist, medical social worker and nurse practitioner for coordination. Tailored evaluation plans for these children using validated tools were designed based on current institutional protocols and prevailing guidelines.

All survivors of ASO for TGA were included for the study. Those who underwent ASO as part of double switch operation, or palliative ASO as for univentricular physiology with subaortic obstruction were excluded from the study. Details of initial surgery and data regarding the intra and perioperative period were extracted from the electronic medical records. The “first postoperative lactate level” referred to the first value on shifting to the intensive care. “Time to lactate normalization” was defined as the time from first postoperative blood gas analysis to the ABG in which the lactate value <2 mmol/L.

Cardiovascular status was evaluated clinically and using electrocardiograms and transthoracic echocardiography. Cardiac magnetic resonance imaging (MRI) and computed tomography were done in select cases as per clinical indications. Anthropometric indices were measured, and growth parameters calculated using the World Health Organization ANTHRO software (version 3.2.2, January 2011, WHO, Geneva, Switzerland).

A pediatric neurologist evaluated patients for developmental delay, neuromotor impairment, seizures, and other neurological deficits. Clinical psychologist administered Trivandrum Development Screening Chart (TDSC) for assessing developmental delay and

developmental quotient (DQ) was calculated clinically using the formula child's developmental age/chronological age x100. Children were classified to be normal (≥85), mild-moderate impairment (≥55 to <85) and severe impairment (<55) based on DQ. INCLEN diagnostic tool for attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder, maladaptive behavioral index for behavioral problems, Vineland adaptive behavior scale (VABS) scale-third edition (interview form) for adaptive functions and Vineland social maturity scale (VSMS) for social quotient were the other standardized tests administered for assessment of neurodevelopmental outcome. The social quotient was considered to be low when the value was ≤70. Speech and language problems were identified using Receptive-Expressive Emergent Language Test second edition, assessment of language development and Malayalam diagnostic articulation test. Screening for hearing and visual impairment and sensory profiling by Winnie and Dunn was done in all patients. Children with autism spectrum disorder, ADHD, developmental delay, maladaptive behavior, neuromotor impairment, speech and language disorder and hearing and visual impairment were considered to have neurodevelopmental disorder (NDD).

HRQOL was calculated from parent filled questionnaires of the PedsQL 3.0 Cardiac Module. The socioeconomic status index was arrived at follow-up for the families using the Modified Kuppuswamy scale (2019) and its impact on the outcomes were studied.

15. Detailed analysis of results :

A total of 68 children were operated during this period; there were 61 survivors (89.70%) at a mean follow-up period of 48±11 months. Three children died in hospital due to sepsis and four children were lost to follow up. The children hailed from Kerala and Tamil Nadu states of south India.

The baseline characteristics of the study cohort are presented in **table 1**. Thirty-one children (49.2%) had TGA-IVS, 23 (36.5%) had TGA-VSD and seven (11.1%) had Taussig Bing anomaly. Balloon atrial septostomy was done in 29 children at a median 10 days of life, and 5 days of life in TGA-IVS. The median age at ASO was 41 days [22-74.5]. Three patients had aortic arch hypoplasia requiring arch repair. The operative technique and perioperative management protocols remained the same during the period assessed except for the type of cardioplegia solution which changed from St Thomas solution to the Del Nido solution. All children with TGA -IVS in the study underwent primary ASO. There were no instances of left ventricular retraining and secondary ASO in the study period. No patient needed ventricular assist devices, extracorporeal circulatory support or heart transplantation in this series.

Cardiovascular outcomes: One child had progressive severe left pulmonary artery stenosis. Another child had supravalvar neo-pulmonary artery stenosis. Both underwent pulmonary angioplasty. Two children had mild left ventricular dysfunction. Both belonged to the TGA-VSD group. Four children had moderate neo-aortic regurgitation on follow up, and were kept on medical follow up.

General Growth and Nutritional status at follow-up: The mean body mass index at follow-up was 14.4±1.9 kg/m^2. The z-scores of weight-for-age, height-for-age, and weight-for-height were -1.53±1.49, 0.94±1.08, and 1.43±1.63 respectively. As per WHO classification, 18% were moderately underweight and 4.9% were severely underweight and 14.8% and 3.3% were moderately and severely stunted respectively, reflective of chronic malnutrition. Ten children

(16.4%) had moderate wasting and one child was severely wasted. None were overweight or obese. Eight children had facial dysmorphism. Four patients had microcephaly. Low weight-for-age, low height-for-age, or low weight-for-height was not associated with developmental delay (p=0.30, p=0.34 and p=0.54 respectively).

Neurological outcomes: Neurological abnormalities were seen in 19 patients (31.1%) of which 17 patients had NDD (27.9%). Twelve children had neurodevelopmental delay. Adaptive and language domains showed faltering when compared to motor domains. A higher first postoperative lactate value and increasing time to lactate normalization were associated with language delay (p=0.001, 0.005 respectively). Seven patients had perioperative seizures. Three of them (4.9%) had recurrence of seizures on follow-up and their scalp electroencephalogram showed epileptiform abnormalities. Three patients had disabling behavioral issues and one child had hearing and visual impairment.

Among the four children who had neuromotor impairment, two had infantile hemiparesis and one patient each had generalized hypotonia and appendicular spasticity. On gross motor functional classification system, only one patient was in level V (not able to sit or stand independently) and two patients were in level II (requires the help of railings to climbs stairs) and rest were able to run and climb stairs without any assistance (level I).

Abnormalities on MRI brain were identified in two children with neuromotor impairment. One had a large porencephalic cyst in the left cerebral hemisphere. Periventricular white matter involvement was identified in the other patient.

In TGA-IVS, there was no difference in neurodevelopmental outcomes in those who underwent ASO beyond three weeks of life as opposed to those who underwent ASO earlier. Age at surgery was not associated with developmental delay in TGA-VSD group either. The neurodevelopmental outcomes in the ten children who underwent ASO in the first two weeks of life was similar to those operated later.

Quality of life: The mean HRQOL was >90 in all scales of the Pediatric Quality of Life Inventory™ 3.0 Cardiac Module.

Developmental outcomes analysis:

The factors associated with neurodevelopmental delay were studied. Univariate analysis suggested that first postoperative lactate level and time to lactate normalization were associated with adverse neurodevelopmental outcome after ASO. Low socioeconomic status and longer stay in the intensive care showed a trend towards suboptimal neurodevelopmental outcomes on univariate analysis. On multivariate analysis, increasing time to lactate normalization and low socioeconomic status were found to be associated with developmental delay after ASO. Cardiac function, neurological outcome and HRQOL were comparable between TGA-IVS and TGA-VSD groups.

Parameter	**Total (61)**	**Normal (49)**	**Neurodevelopmental delay (12)**
Birth weight (kg), mean ± SD	2.9 ± 0.6	2.9 ± 0.6	2.9 ± 0.7

Gender ratio (males:females)	2.58:1		2.5:1		3:1	
Mother's age at conception (years), mean ± SD	25.6 ± 4.9		25.8 ± 5.2		25.1 ± 3.2	
Educational status, n (%)	**Mother**	**Father**	**Mother**	**Father**	**Mother**	**Father**
	0	0	0	0	0	0
• Illiterate	3 (4.8)	12 (19.0)	3 (6.1)	10 (20.4)	0	2 (16.7)
• Primary school	21 (33.3)	24 (38.1)	18 (36.7)	18 (36.7)	3 (25)	6 (50)
• High school	21 (33.3)	16 (25.4)	15 (30.6)	13 (26.5)	6 (50)	3 (25)
• Higher secondary school	14 (22.2)	8 (12.7)	11 (22.4)	7 (14.3)	3 (25)	1 (8.3)
• Graduate	2 (3.2)	1 (1.6)	2 (4.1)	1 (2.0)	0 (0)	0 (0)
• Postgraduate or higher						
Occupation, n (%)	**Mother**	**Father**	**Mother**	**Father**	**Mother**	**Father**
• Unemployed	50 (82)	0	40 (81.6)	0	10 (83.3)	0
• Unskilled labor	0	11 (18)	0	6 (12.2)	0	5 (45.5)
• Semi-skilled	1 (1.6)	30 (49)	0	8 (16.3)	1 (8.3)	0
• Skilled worker	5 (8.2)	5 (8)	4 (8.2)	30 (61.2)	1 (8.3)	6 (54.6)
• Office jobs	5 (8.2)	14 (23)	5 (10.2)	5 (10.2)	0	0
Monthly family income (Rs), median [IQR]	10,000 [5,000-20,000]		10,000 [5,000-20,000]		7,500 [4,250-16,500]	
Kuppuswamy socioeconomic class, n (%)						
• Lower	1 (1.6)		0		1 (8.3)	
• Upper lower	27 (42.9)		21 (41.9)		6 (50)	
• Lower middle	23 (36.5)		19 (38.8)		4 (33.3)	
• Upper middle	10 (15.9)		9 (18.4)		1 (8.3)	
• Upper	0		0		0	
Diagnostic classes						
• TGA intact ventricular septum	31 (49.2)		25 (51)		6 (50)	
• TGA-VSD	23 (36.5)		20 (40.8)		3 (25)	
• Taussig Bing	7 (11.1)		4 (8.2)		3 (25)	

Lowest preoperative saturation (%), mean ± SD	65.4 ± 16.0	66 ± 15.8	62 ± 17.4
Immediate preoperative saturation (%),mean ± SD	75.7 ± 8.4	76.1 ± 8.1	73.8 ± 9.7
BAS, n (%)	29 (47.5)	23 (46.9)	6 (50)
Surgery performed, n (%) • ASO • ASO with VSD closure • ASO, VSD closure, arch repair • ASO with LVOT resection	30 (49.2) 25 (41) 3 (4.9) 3 (4.9)	24 (49) 21 (42.9) 2 (4.1) 2 (4.1)	6 (50) 4 (33.3) 1 (8.3) 1 (8.3)
Age at surgery (days), median [IQR] • TGA intact ventricular septum • TGA-VSD • Taussig Bing	41 [22,75.5] 23 [13,40] 65 [42,108] 63 [59,174]	40 [20.5,77] 22 [13,39] 68 [42.5,105] 118.5 [33,226.5]	44 [22.5,62.3] 33.5 [19.5,42.5] 63 (117)* 60 (16)*
CPB time (minutes), mean ± SD	247.73 ± 72.90	241.6 ± 54.5	268.0 ± 124.3
Aortic cross clamp time (minutes), mean ± SD	150.83 ± 39.92	150.3 ± 36.9	153.2 ± 52.5
Coronary artery pattern • 1LCx2R • 1L2RCx • 2LCx1R • 1Cx2LR • Single coronary from right sinus • Single coronary from left sinus	 40 (65.57) 10 (16.39) 5 (8.19) 1 (1.63) 3 (4.92) 1 (1.63)		
LV regression, n (%)	11 (18.0)	8 (16.3)	3 (25)

	Cardioplegia, n (%) • St Thomas solution • Del nido solution	51 (83.6) 10 (16.4)	43 (87.8) 6 (12.2)	8 (66.7) 4 (33.3)
	Primary chest closure, n (%)	3 (4.9)	2 (4.1)	1 (8.3)
	Modified ultrafiltration, n (%)	58 (95.1)	47 (95.9)	11 (91.7)
	Duration till delayed sternal closure (hours), mean ± SD	34.6 ± 22.9	34.8 ± 23.8	33.6 ± 19.7
	Duration of ICU stay (days), mean ± SD	10 ± 4.4	9.80 ± 4.27	11.1 ± 4.9
	Duration of mechanical ventilation (hours), mean ± SD	88.31 ± 58.95	84.9 ± 55.8	102.4 ± 71.5
	1st postoperative arterial lactate, mean ± SD	2.99 ± 1.6	2.7 ± 1.1	4.1 ± 2.8
	Time to lactate normalization (hours), mean ± SD	57.8 ± 45.8	51.2 ± 39.1	84.6 ± 61.8
	Vasoactive inotropic score, mean ± SD	8.67 ± 4.15	8.1 ± 3.2	11.1 ± 6.2
	Peritoneal dialysis, n (%)	9 (14.8)	7 (14.3)	2 (16.7)
	Blood stream infections, n (%)	8 (13.1)	8 (16.3)	0
	Duration of follow up (months), mean ± SD	46.2 ± 8.5	46.3 ± 8.4	45.6 ± 2.7
	Age at last follow up (months), mean ± SD	50.93 ± 7.6	51.2 ± 7.5	49.7 ± 8.5
16.	**Summary sheet of not more than 2 pages under following heads :** **(Title, Introduction, Rationale, Objectives, Methodology, Results, Translational Potential)**			
	Title: Evaluation of intermediate term cardiac and neurodevelopmental outcomes of children undergoing corrective arterial switch operation for complete transposition of great arteries			

	Introduction: Advances in surgical techniques and perioperative care have significantly lowered the mortality rates for children and adolescents with complex congenital heart disease (CHD) over the past several decades. The focus of research has paralleled this population shift and changed from surgical survival alone to the assessment of long-term morbidity especially the developmental aspects. **Rationale:** Survivors of cardiac surgery may need close follow-up for developmental outcomes, before they are comparable to the general population. Mild neurological abnormality was observed in children who underwent ASO and intelligence quotient was related to paternal education, perioperative neurologic abnormalities, birth weight, and circulatory arrest time. **Objectives:** The study objective was to evaluate the cardiac, neurodevelopmental, psychosocial and health related quality of life (HRQOL) outcomes of children who underwent an arterial switch operation (ASO). **Methodology:** A cross-sectional study of children who have undergone corrective arterial switch operation under cardiopulmonary bypass in infancy for complete Transposition of great vessels between 2014 and 2015 at SCTIMST for evaluation for their cardiovascular and neuro-developmental outcomes based on routine examination and questionnaire-based interaction. **Results:** There were 61 (89.7%) survivors at a mean follow-up of 50.9± 7.6 months. The median age at surgery was 41 days [22-74.5]. One-third of patients had growth restriction. Two children had residual cardiovascular lesions requiring intervention. Mean HRQOL score was >90 in all scales of the Pediatric Quality of Life Inventory™ 3.0 Cardiac Module. Neurological abnormalities were seen in 19 patients (31.1%) of which 17 (27.9%) patients had NDD and 12 had developmental delay. Speech and language impairment, attention-deficit hyperactivity disorder, neuromotor and hearing impairment was found in 16.4%, 3.3% and 6.7% patients respectively. On multivariate analysis, increasing time to lactate normalization and low socioeconomic status were associated with developmental delay after ASO. Excellent quality of life was observed in the majority of children after arterial switch operation with the median total PedsQL scores in all domains of 97.9. **Translational potential:** This study demonstrates the excellent outcomes after arterial switch operation for transposition of the great arteries based on survival outcomes, neurodevelopmental outcomes, and quality of life measures at pre-school age. This study forms the benchmark for long-term follow-up and continued surveillance of survivors of complex cardiac surgeries in infancy.
17.	**Contributions made towards increasing the state of knowledge in the subject :**
	This study demonstrates the excellent outcomes after arterial switch operation for transposition of the great arteries based on survival outcomes, neurodevelopmental outcomes, and quality of life measures at pre-school age. This study forms the benchmark for long-term follow-up and continued surveillance of survivors of complex cardiac surgeries in infancy.
18.	**Conclusions summarising the achievements and indication of scope for future work :**
	While intermediate term cardiac outcomes and HRQOL after ASO is satisfactory, neurodevelopmental disorder was identified in one-fourth of these children. Speech and language was the most common domain affected. Increasing time to lactate normalization after ASO and low socioeconomic status are associated with neurodevelopmental delay after ASO. This study highlights the need for a structured neurodevelopmental screening using standardized assessment scales by a multidisciplinary team to detect neurodevelopmental disorders in survivors of complex cardiac surgery. This will give us an opportunity for early identification and appropriate intervention. Excellent quality of life was observed in the majority of children after arterial switch operation with the median total PedsQL scores in all domains of 97.9.

19.	**Science and Technology benefits accrued :**				
	a.	**List of research publications with complete details :**			
		1. Ramanan S, Sundaram S, Gopalakrishnan A, Anija DV, Sandhya P, Jose DS, Baruah SD, Menon S, Dharan BS. Intermediate-term neurodevelopmental outcomes and quality of life after arterial switch operation. **Eur J Cardiothorac Surg** 2021 Jun 21;ezab223. doi: 10.1093/ejcts/ezab223. Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/34151942/ 2. Ramanan S, Gopalakrishnan A, Sundaram S, Varma RP, Gopakumar D, Viswam VK, Satheesan R, Baruah SD, Menon S, Dharan BS. Pediatric Quality of Life in toddlers and children who underwent arterial switch operation beyond early neonatal period. **Eur J Cardiothorac Surg**. 2023 Sep 19:ezad321. doi: 10.1093/ejcts/ezad321. Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/37725365/			
	b.	**Manpower trained on the project :**			
		i.	**Research Scientists or Research Fellows**	**:**	**1**
		ii.	**No. of PhD's produced**	**:**	**0**
		iii.	**Other Technical Personnel trained**	**:**	**4**
	c.	**Patents taken, if any**		**:**	**Nil**
	d.	**Products developed, if any**		**:**	**Nil**
20.	**Abstract: (In 300 words for possible publication in ..... Bulletin)**				
	a.	**Background:**			
		Advances in surgical techniques and perioperative care have significantly lowered the mortality rates for children and adolescents with complex congenital heart disease (CHD) over the past several decades. The focus of research has paralleled this population shift and changed from surgical survival alone to the assessment of long-term morbidity especially the developmental aspects. Advances in surgical techniques and perioperative care have significantly lowered the mortality rates for children and adolescents with complex congenital heart disease (CHD) over the past several decades. The focus of research has paralleled this population shift and changed from surgical survival alone to the assessment of long-term morbidity especially the developmental aspects.			
	b.	**Materials:**			
		The study objective was to evaluate the cardiac, neurodevelopmental, psychosocial and health related quality of life (HRQOL) outcomes of children who underwent an arterial switch operation (ASO). A cross-sectional study of children who have undergone corrective arterial switch operation under cardiopulmonary bypass in infancy for complete Transposition of great vessels between 2014 and 2015 at SCTIMST for evaluation for their cardiovascular and neuro-developmental outcomes based on routine examination and questionnaire-based interaction.			
	c.	**Results:**			
		There were 61 (89.7%) survivors at a mean follow-up of 50.9± 7.6 months. The median age at surgery was 41 days [22-74.5]. One-third of patients had growth restriction. Two children had residual cardiovascular lesions requiring intervention. Mean HRQOL score was >90 in all scales of the Pediatric Quality of Life Inventory™ 3.0 Cardiac Module. Neurological abnormalities were seen in 19 patients (31.1%) of which 17 (27.9%) patients had NDD and 12 had developmental delay. Speech and language impairment, attention-deficit hyperactivity disorder, neuromotor and hearing impairment was found in 16.4%, 3.3% and 6.7% patients respectively. On multivariate analysis, increasing time to lactate normalization and low socioeconomic status were associated with developmental delay after ASO. Excellent quality of life was observed in the majority of children after arterial switch operation with the median total PedsQL scores in all domains of 97.9.			

	d.	**Conclusion:**
		While intermediate term cardiac outcomes and HRQOL after ASO is satisfactory, neurodevelopmental disorder was identified in one-fourth of these children. Speech and language was the most common domain affected. Increasing time to lactate normalization after ASO and low socioeconomic status are associated with neurodevelopmental delay after ASO. This study highlights the need for a structured neurodevelopmental screening using standardized assessment scales by a multidisciplinary team to detect neurodevelopmental disorders in survivors of complex cardiac surgery. This will give us an opportunity for early identification and appropriate intervention. Excellent quality of life was observed in the majority of children after arterial switch operation with the median total PedsQL scores in all domains of 97.9.
21.	**Procurement/Usage of Equipment:**	
	a.	**Details of Equipment:**

		Sl. No.	**Name of Equipment**	**Make/ Model**	**Cost (Rs.)**	**Date of Installation**	**Utilisation**	**Remarks regarding maintenance breakdown**
		1	**Laptop**	**HP**	**Rs. 32,900/-**	**21/01/2019**	**Data analysis**	**Nil**

	b.	**Suggestions for disposal of equipment(s):**
		The laptop is being used in the department of CVTS for teaching purposes.

Dr Baiju S Dharan
15 – 11 – 2023
(Name and Signature of PIs with date)

Routing: *Signed copy of "Project completion Report" by PI →* root@sctimst.ac.in, rpc@sctimst.ac.in