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Are early palliative procedures providing an adequate long-term benefit in young cyanotic infants from developing countries, despite advances in surgery and interventions?

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Abstract

Objectives: Ductal stents, right ventricular outflow tract stents, and aortopulmonary shunts are used to palliate newborns and infants with reduced pulmonary blood flow. Current long-term outcomes of these palliations from resource-restricted countries are unknown. *Methods:* This single-centre, retrospective, observational study analysed the technical success, immediate and late mortality, re-interventions, and length of palliation in infants ≤5 kg who underwent aortopulmonary shunts, ductal, and pulmonary outflow stents. Patients were grouped by their anatomy. *Results:* There were 69 infants who underwent one of the palliations. Technical success was 90% for aortopulmonary shunts (n = 10), 91% for pulmonary outflow stents (n = 11) and 100% for ductal stents (n = 48). Early mortality within 30 days in 12/69 patients was observed in 20% after shunts, 9% after pulmonary outflow stents, and 19% after ductal stents. Late mortality in 11 patients was seen in 20% after shunts, 18% after outflow stents, and 15% after ductal stents. Seven patients needed re-interventions; two following shunts, one following outflow stent, and four following ductal stents for hypoxia. Among the anatomical groups, 10/12 patients with pulmonary atresia, intact ventricular septum survived after valvotomy and ductal stenting. Survival to Glenn shunt after ductal stent for pulmonary atresia, intact ventricular septum and diminutive right ventricle was very low in two out of eight patients, but very good (100%) for other univentricular hearts. Among 35 patients with biventricular lesions, 22 survived to the next stage. *Conclusions:* Cyanotic infants, despite undergoing technically successful palliation had a high inter-stage mortality irrespective of the type of palliation. Duct stenting in univentricular hearts and in pulmonary atresia with an intact ventricular septum and adequate sized right ventricle tended to have low mortality and better long-term outcome. Completion of biventricular repair after palliation was achieved only in 63% of patients, reflecting unique challenges in developing countries despite advances in intensive care and interventions.

Blalock–Taussig shunt is associated with significant mortality in young infants.[1] While mortality had decreased in most congenital heart surgeries over the years, shunts show an opposite trend.[2] The current mortality of 9.8% is attributed to smaller patient size and an increasing proportion of single ventricles.[3] Poor outcomes after neonatal repair of the tetralogy of Fallot reiterate the need for safe durable palliation.[4]

Arterial duct stenting is emerging as an alternative to aortopulmonary shunts with comparable risks of death or unplanned interventions.[5,6] It is favoured due to improved survival despite the need for re-interventions.[7] Variable ductal anatomy and confluence stenosis is known to alter the procedural success.[8] Drug-eluting stents reduce neointimal proliferation thereby increasing the duration of palliation and reducing the incidence of unplanned re-interventions, but high serum sirolimus levels raise concerns.[9–11] This concern has been recently addressed by the third generation drug-eluting stents, which have undetectable sirolimus levels after 7 days in most neonates.[12] Aspirin, low-molecular-weight heparin, and clopidogrel have improved the patency of surgical shunts and stents.[13–15]

Stenting of the right ventricular outflow tract is another palliation with shorter hospitalisation, lower mortality, and improved pulmonary arterial growth compared to surgical shunts.[16,17] It is a preferred mode of palliation in hypoplastic pulmonary arteries.[18,19]

Despite significant advances in surgery and interventions, wide global disparities exist in the management of young infants.[20] Outcomes of the different methods of palliation in various anatomical substrates warrant systematic analysis in low-middle-income countries in view of different ground realities when compared to the developed countries. As there is no

multi-institutional database that includes both catheter interventions and surgery, this study aims at a meticulous analysis of the follow-up data of all young patients who have been palliated for reduced pulmonary blood flow.

Methods

A retrospective review of all young infants with critically reduced pulmonary blood flow who underwent a palliative procedure was done after approval from the institutional review board and ethical committee. Parental consent for data retrieval from the hospital records was waived.

Inclusion and exclusion

All young infants weighing less than 5 kg needing a palliation to relieve hypoxia between July, 2013 and June, 2020 were included. Patients who needed surgical repair of the confluence during shunt, concurrent catheter interventions during a ductal stent, a bilateral ductal stent for non-confluent pulmonary arteries were also included. Pulmonary atresia with an intact ventricular septum or critical valvar pulmonary stenosis after balloon pulmonary valvotomy that did not require a shunt or ductal stent was excluded. Palliation for isolation of one of the pulmonary arteries was also excluded.

Choice of palliation

After joint departmental discussions, the choice was based on the clinical details, comorbidities, echocardiographic findings, and laboratory investigations. Other factors that influenced decision-making were the risk profile, anticipated advantages, duration of palliation needed, and parental consent. Patients were analysed on "intention to treat" basis. The ductal stent was preferred for providing additional pulmonary blood flow after neonatal balloon pulmonary valvotomy in the hypoplastic right ventricle.[21] It was also preferred in high-risk surgical anatomy like pulmonary atresia, intact ventricular septum with severely hypoplastic right ventricle, and other univentricular hearts, when a short-term palliation till 6 months was needed before a bidirectional Glenn shunt.[21] It was also performed in some patients, irrespective of the anatomical subset as ductal stenting involved lesser costs of hospitalisations compared to surgical shunts.[22] Pulmonary outflow stent was preferred in the tetralogy of Fallot and others with hypoplastic pulmonary arteries.[23] In biventricular lesions, the shunt was preferred except in high-risk patients with prematurity, intra-uterine growth retardation, major additional congenital anomaly, syndromic infants, sepsis, and unstable cardiac haemodynamics. Significant confluence stenosis also favoured surgical shunt while non-confluent pulmonary arteries favoured bilateral ductal stents.

Data collection

Patients were classified under four anatomical groups for analysis, namely pulmonary atresia intact ventricular septum with well-developed right ventricle and severely hypoplastic right ventricle, other univentricular hearts, and patients with biventricular cardiac anatomy. Demographic data included age, birth weight, weight at the time of intervention, antenatal diagnosis with in-utero transfer, prematurity, intra-uterine growth retardation, birth asphyxia, syndromes, other anomalies, and comorbidities. Haemodynamic stability was assessed by oxygen saturations, need for prostaglandin infusion and its duration, need for ventilatory support, if the procedure was an emergency, whether the pulmonary blood flow was solely duct dependent or there was an additional antegrade pulmonary blood flow.

Echocardiographic details included anatomical diagnosis, the confluence of pulmonary arteries, size of pulmonary arteries, z score and Nakata Index, patency of the duct, and its morphological type.[24,25] Procedural details included the size of the surgical shunt, number and diameter of the ductal, or outflow stents.

Post-procedural data included the increase in oxygen saturations, duration of intensive care stay and hospitalisation, acute major complications including hypotension, sepsis, hypoxemia, vascular complications and others, mortality and its causes and need for pre-discharge re-interventions. Post-discharge data included inter-stage mortality, late re-interventions, duration to the final palliation, need for pulmonary arterioplasty, final pulmonary artery size, z score, and Nakata Index.

Outcome indicators

Technical success was defined as the successful completion of the intended procedure. Early mortality was defined as deaths within 30 days and before discharge. Late mortality was deaths after discharge and before the next definitive palliation or surgical correction. Early and late re-interventions were defined as the adoption of an alternative palliative strategy before or after discharge, respectively.

Statistical analysis

Continuous variables were expressed as mean with standard deviation or median with range. Categorical variables were expressed as frequencies or proportions. Comparisons were made on an intention to treat basis between surgical shunt, ductal and outflow stent group. The chi-square test was used for categorical variables. One-way ANOVA was used for comparison of continuous variables in normal distribution between the groups and Kruskal–Wallis test was applied for continuous variables with skewed distribution. The composite outcome was mortality or re-interventions before the final planned surgery. The composite outcome was analysed using the Kaplan–Meier method for survival with 95% confidence intervals. For all tests, a p value of <0.05 was considered statistically significant.

Results

Among 69 young infants weighing less than 5 kg who were palliated for severe hypoxemia, the initial planned procedure was surgical shunt in 10 patients, outflow stent in 11 patients, and ductal stent in the rest (Fig 1). The demographic details, haemodynamic stability, and anatomical diagnosis were compared in Table 1. The acute procedural outcomes were compared in Table 2 and post-discharge follow-up data were compared in Table 3.

Differences between the groups

The ductal stent group more often had an antenatal diagnosis and in utero transfer compared to the other groups. Hence, they were significantly younger and received prostaglandin more often than the surgical shunts. Seventy-nine percent of the ductal stent group had exclusive duct-dependent pulmonary blood flows compared to 19% in the other groups (Table 1). The ductal stent group included significantly more univentricular lesions than others and accounted for all patients with pulmonary atresia with an

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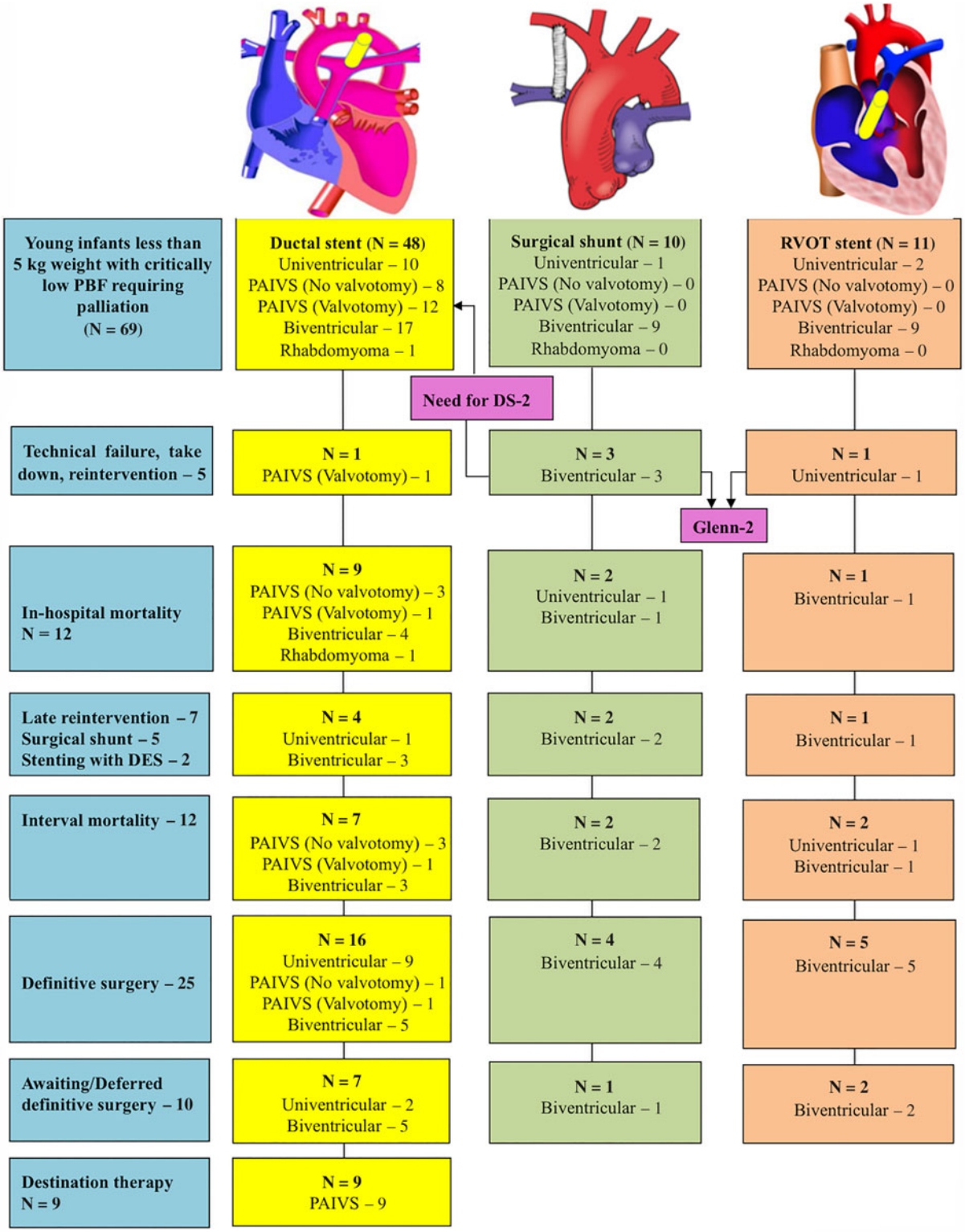

Figure 1. Outcomes after different methods of palliation. The flow chart depicts the technical success, in-hospital and inter-stage mortality, early and late re-interventions, and a number of patients who reached final corrective surgery after the different modes of palliation namely surgical shunt, ductal stent, and right ventricular outflow tract stent.

intact ventricular septum. Biventricular lesions accounted for 90% of surgical shunts and 82% of outflow stents but only 35% of ductal stents (Fig 1). Nine patients with tetralogy of Fallot, one with tricuspid atresia and one with a single ventricle underwent outflow tract stenting. Being a preferred strategy in hypoplastic pulmonary arteries, the pulmonary artery z scores in the outflow stent group were significantly smaller than the others (Table 1). The length of intensive care stay after surgical shunt was significantly longer compared to other modalities of palliation. Although the hospital stay was also longer, the difference did not reach statistical significance (Table 2). The increase in oxygen saturations was higher after ductal stent compared to other groups.

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Table 1. Comparison between three groups

Baseline parameters*	Total (N = 69)	Ductal stent (N = 48)	RVOT stent (N = 11)	Shunt surgery (N = 10)	p value
Median age (days)	13 (1–202)	9 (1–202)	65 (2–158)	50.5 (5–107)	**0.004****
Age < 30 days	46 (66.7)	39 (81.3)	3 (27.3)	4 (40)	<**0.001**
Gender (male:female)	41 (60.3):27 (39.7)	28 (58.3):20 (41.7)	4 (36.4):7 (63.6)	9 (90):1 (10)	**0.042**
Birth weight (kg)	2.7 ± 0.5 (1.26–3.69)	2.79 ± 0.5 (1.3–3.7)	2.54 ± 0.5 (1.8–3.4)	2.47 ± 0.6 (1.5–3.3)	0.120***
Low birth weight <2.5 kg	21 (30.4)	11 (22.9)	5 (45.5)	5 (50)	0.119
Prematurity <37 weeks	11 (15.9)	7 (14.6)	0	4 (40)	0.039
Weight at procedure (kg)	3.14 ± 0.7 (1.46–4.8)	3.08 ± 0.7 (1.97–4.8)	3.46 ± 0.8 (2.4–4.8)	3.08 ± 0.9 (1.46–4.58)	0.301***
Body surface area (m^2)	0.21 ± 0.03 (0.12–0.29)	0.20 ± 0.03 (0.16–0.29)	0.22 ± 0.04 (0.16–0.28)	0.20 ± 0.04 (0.12–0.27)	0.526**
Antenatal diagnosis	21 (30.4)	19 (39.6)	1 (9.1)	1 (10)	0.044
In utero transfer	15 (21.7)	14 (29.2)	0	1 (10)	0.066
Co-morbidities					
Birth asphyxia	4 (5.8)	3 (6.3)	1 (9.1)	0	0.653
Syndrome DiGeorge Pierre Robin Unidentified	5 (7.2) 3 (4.3) 1 (1.4) 1 (1.4)	3 (6.3) 1 (2.1) 1 (2.1) 1 (2.1)	1 (9.1) 1 (9.1)	1 (10) 1 (10)	0.887
Other anomalies	2 (2.9)	1 (2.1)	1 (9.1)	0	0.385
Pre-procedural haemodynamic status					
Oxygen saturation %	63.37 ± 9.6 (40–86)	62.42 ± 8.8 (50–80)	67.18 ± 12.3 (40–86)	63.44 ± 9.4 (50–74)	0.340***
PGE1 use	33 (47.8)	28 (58.3)	2 (18.2)	3 (30)	**0.026**
Median PGE1 duration	72 (24–408) hours	72 (24–408) hours	60 (24–96) hours	72 (48–96) hours	0.878**
Pre-operative ventilation	12 (17.4)	9 (18.8)	1 (9.1)	2 (20)	0.727
Emergency procedure	13 (18.8)	6 (12.5)	4 (36.4)	3 (30)	0.117
Anatomical diagnosis					**0.004**
TOF	13 (18.8)	3 (6.3)	8 (72.7)	2 (20)	
TOF, PA	11 (15.9)	7 (14.6)	0	4 (40)	
DORV/DOLV PS	8 (11.6)	6 (12.5)	1 (9.1)	1 (10)	
PAIVS – diminutive RV	7 (10.1)	7 (14.6)	0	0	
PAIVS – adequate RV	8 (11.6)	8 (16.7)	0	0	
Critical valvar PS	5 (7.2)	5 (10.4)	0	0	
DTGA VSD PS	3 (4.3)	1 (2.1)	0	2 (20)	
LTGA VSD PS or PA	4 (5.8)	4 (8.3)	0	0	
Single ventricle	3 (4.3)	2 (4.2)	1 (9.1)	0	
Tricuspid atresia	6 (8.7)	4 (8.3)	1 (9.1)	1 (10)	

(*Continued*)

Table 1. (*Continued*)

Baseline parameters*	Total (N = 69)	Ductal stent (N = 48)	RVOT stent (N = 11)	Shunt surgery (N = 10)	p value
RV rhabdomyoma	1 (1.4)	1 (2.1)	0	0	
Pulmonary flow	41 (59.4)	37 (77.1)	0	4 (40)	<**0.001**
Solely duct dependent	28 (40.6)	11 (22.9)	11 (100)	6 (60)	
Antegrade flow present					
Pulmonary artery size					
RPA (mm)	4.34 ± 1.1 (1–7)	4.5 ± 1.1 (2.6–7)	3.82 ± 1.3 (1–6)	4.16 ± 1.3 (2.5–7)	0.172***
LPA (mm)	4.25 ± 1.2 (1–7)	4.5 ± 1.0 (2–7)	3.54 ± 1.4 (1–6.5)	4 ± 1.4 (2.5–7)	**0.040****
RPA z score	−0.6 ± 1.7 (−8.6 to +2.9)	−0.2 ± 1.4 (−3.0 to +2.9)	−1.7 ± 2.7 (−8.62 to +2.1)	−1 ± 1.3 (−3.6 to1.7)	**0.018****
LPA z score	−0.3 ± 1.8(−8.1 to +2.9)	0.2 ± 1.3 (−4.17 to +2.9)	−1.8 ± 2.7(−8.13 to +2.9)	−0.8 ± 1.7(−3.1 to 2.2)	**0.002****
Nakata Index	151.6 ± 71.6 (10–367)	163.5 ± 63.4 (47–339)	113.9 ± 92.1 (10–367)	135.6 ± 74.3 (49–296)	0.086***
Non-confluence/stenosis	12 (17.6)	10 (21.3)	2 (18.2)	0	0.286
Absence of confluence	2	2	0	0	
Confluence stenosis	10	8	2	0	
Ductal patency (56)	56 (81.2)	48 (100)	2 (18.2)	6 (60)	<**0.001**
Ductal morphology	16 (28.6)	16 (33.3)	0	0	
Usual duct origin: Type I	8 (14.3)	5 (10.4)	0	3 (50)	
Vertical duct: Type II	25 (44.6)	20 (41.7)	2 (100)	3 (50)	
Tortuous duct: Type III	5 (8.9)	5 (10.4)	0	0	
Contralateral duct: Type IV	2 (3.6)	2 (4.2)	0	0	
Bilateral duct: Type V					

DOLV = double-outlet left ventricle; DORV = double-outlet right ventricle; DTGA = d-transposition of great arteries; IVS = intact ventricular septum; LPA = left pulmonary artery; LTGA = l-transposition of great arteries; PA = pulmonary atresia; PGE1 = prostaglandin E1; PS = pulmonary stenosis; RPA = right pulmonary artery; RV = right ventricle; RVOT = right ventricular outflow tract; TOF = tetralogy of Fallot; VSD = ventricular septal defect

Bold fonts indicate statistical significance with $p < 0.05$

*Data expressed in frequency (percentage) for nominal data, mean ± SD (range) for a continuous variable in a normal distribution, median (range) for continuous variables in the non-normal distribution

**Kruskal–Wallis test

***One-way ANOVA; chi-square for nominal

Table 2. The procedural outcome of the three groups

Procedural outcomes	**Total (N = 68)**	**Ductal stent (N = 48)**	**Rvot stent (N = 11)**	**Surgical shunt (N = 10)**	p value
Diameter of stent or shunt	4.0 ± 0.76 (2.75–8)	3.86 ± 0.32 (2.75–4.5)	4.95 ± 1.42 (4–8)	3.61 ± 0.33 (3–4)	<0.001*
Technical success	67 (97.1)	48 (100)	10 (91)	9 (90)	0.094
Oxygen saturation after procedure	87.23 ± 6.2 (70–99)	88.87 ± 4.94 (78–99)	84.78 ± 6.20 (76–95)	81.33 ± 8.13 (70–90)	0.001*
Acute major complication	25 (36.2)	15 (31.3)	3 (27.3)	7 (70)	**0.054**
Technical failure	2	0	1	1	
Hyperperfusion needing takedown/clip	3	1	0	2	
Hyperperfusion managed medically	2	2	0	0	
Retroperitoneal haematoma	3	3	0	0	
Sepsis	9	5	1	3	
Low cardiac output	5	3	1	1	
Need for emergency Glenn surgery	2	0	1	1	
Switch to other palliation	1	0	0	1	
Early re-intervention	1	0	0	1	
Pre-discharge in-hospital mortality	12 (17.4)	9 (18.8)	1 (9.1)	2 (20)	0.727
Median intensive care duration (days)	2 (0–35)	2 (0–25)	1 (0–9)	7.5 (1–35)	**0.011****
Median hospital stay (days)	7 (2–50)	7 (2–30)	5 (2–17)	14 (2–50)	0.136**

RVOT = right ventricular outflow tract
Bold fonts indicate statistical significance with $p < 0.05$
Data expressed in frequency (percentage) for nominal data, mean ± SD (range) for continuous variable in normal distribution, median (range) for continuous variables in non-normal distribution
*One-way ANOVA
**Kruskal–Wallis test; chi-square for nominal

Table 3. The post-procedural follow-up in the three groups

Follow-up data	**Total (N = 57)**	**Ductal stent (N = 39)**	RVOT stent (N = 10)	**Surgical shunt (N = 8)**	p value
Post-discharge interval mortality	12 (21.1)	8 (20.5)	2 (20)	2 (25)	0.957
Re-intervention	7 (12.3)	4 (10.3)	1 (10)	2 (25)	0.497
Surgical shunt	5	2	1	2	
Repeat ductal stent	2	2	0	0	
Pulmonary artery size before surgery	n = 28	n = 19	n = 5	n = 4	–
Right pulmonary artery on follow-up	8.3 ± 1.8 (5–12.5)	8.8 ± 1.78 (6.4–12.5)	7.1 ± 1.43 (5–9)	7.4 ± 1.9 (5–9.2)	0.101*
Left pulmonary artery on follow-up	8.2 ± 2.2 (5–14)	8.2 ± 2.31 (5–14)	7.7 ± 1.92 (6–11)	8.6 ± 2.1 (6–10.5)	0.824*
Right pulmonary artery z score	1.3 ± 1.3 (−1.7 to 4.3)	1.6 ± 1.2 (−0.3 to 4.3)	0.5 ± 1.3 (−1.7 to 1.7)	0.8 ± 1.9(−1.5 to 2.7)	0.201*
Left pulmonary artery z score	1.7 ± 1.3 (−0.4 to 4.3)	1.6 ± 1.3 (−0.43 to 3.9)	1.6 ± 1.3 (0.12–3.5)	2.3 ± 1.7 (0.2–4.3)	0.664*
Nakata Index on follow-up	287.9 ± 105.7 (130–543)	302.8 ± 101.4 (156–543)	247.2 ± 98.8 (130–397)	268.3 ± 145.3 (137–476)	0.551*
Pulmonary artery symmetry index	0.86 ± 0.12 (0.5–1)	0.82 ± 0.15 (0.5–1)	0.93 ± 0.09 (0.8–1)	0.86 ± 0.05 (0.8–0.9)	0.334*
Completion of next surgery	27 (48.2)	16 (42.1)	6 (80)	5 (62.5)	0.411
Branch PA stenosis during surgery	14 (51.9)	12 (75)	1 (16.7)	1 (20)	**0.015**
Need for PA plasty during surgery	16 (59.3)	14 (87.5)	1 (16.7)	1 (20%)	**0.002**
Length of palliation to next surgery(months)	10 (0.03–27)	9.5 (5–27)	11 (0.03–15)	11 (0.1–20)	0.689**
Number of patients awaiting surgery	11	8	2	1	–

PA = pulmonary artery; RVOT = right ventricular outflow tract
Bold fonts indicate statistical significance with $p < 0.05$
Data expressed in frequency (percentage) for nominal data, mean ± SD (range) for a continuous variable in a normal distribution, median (range) for continuous variables in the non-normal distribution
*One-way ANOVA
**Kruskal–Wallis test; chi-square for nominal

Technical success

Technical success was 90% among the 10 surgical shunts. Severe hypoxia on trial clamping of the pulmonary artery in one neonate with tetralogy and pulmonary atresia did not allow proceeding with the shunt and warranted a ductal stent. The success of outflow stenting in 11 patients was 91%. One patient with asplenia syndrome, univentricular heart, and hypoplastic pulmonary arteries developed outflow tear and was managed successfully by emergent

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Table 4. The outcome after different palliation in each anatomical group

Type of Palliation	Anatomical group	Number of patients	Technical success	Early deaths	Re-intervention	Late death	Survival	Duration to next surgery
Ductal stent	All groups	48	100%	9	7	7	32 (67%)	9.5 (5–27) months
	PAIVS well-developed RV	12	100%	1	1	1	10 (83%)	42 (3–72) months
	PAIVS severely hypo-plastic RV	8	100%	3	0	3	2 (25%)	7 months
	Other univentricular hearts	10	100%	0	0	0	10 (100%)	10 (6–24) months
	Biventricular hearts	17	100%	4	6	3	10 (59%)	10 (6–27) months
	Rhabdomyoma	1	100%	1	0	0	0	–
Surgical shunt	All groups	10	90%	2	3	2	6 (60%)	–
	Univentricular hearts	1	100%	1	0	0	0	–
	Biventricular hearts	9	89%	1	3	2	6 (67%)	11 (0.1–20) months
RVOT stent	All groups	11	91%	1	1	2	8 (73%)	–
	Univentricular heart	2	50%	0	0	1	1 (50%)	–
	Biventricular heart	9	100%	1	1	0	8 (89%)	11 (0.03–15) months

PAIVS = pulmonary atresia intact ventricular septum; RV = right ventricle; RVOT = right ventricular outflow tract

Glenn shunt. Technical success was 100% after ductal stenting (Table 4).

Early in-hospital mortality

Early mortality within 30 days in 12/69 patients was observed in 20% after shunts, 9% after pulmonary outflow stents, and 19% after ductal stents. Early death after a 3.5-mm shunt due to refractory hypotension and low cardiac output included the lone univentricular patient aged 45 days with tricuspid atresia and hypoxic spells and another 3-month-old infant with tetralogy of Fallot. Early death after a 4-mm outflow stent for severely hypoplastic pulmonary arteries in a 1-month-old infant with tetralogy of Fallot and multiple aortic collaterals was possibly due to pulmonary over-circulation within few hours and documented stent patency (Table 5). Among nine deaths after ductal stenting, five deaths directly related to the procedure were caused by retroperitoneal haematoma in two patients and pulmonary over-circulation in three patients. The haemodynamic compromise from retroperitoneal haematoma was not tolerated due to a low body weight of 1.6 kg in one and perinatal birth asphyxia in the other. Pulmonary over-circulation occurred in two with pulmonary atresia with an intact ventricular septum and one with Fallot's tetralogy with pulmonary atresia. Closure of the ductal stent with a plug after 2 days in one patient with over-circulation did not result in clinical improvement. Four patients had unrelated death due to persistent sepsis after 21 days in one, necrotising enterocolitis and liver abscess after 6 days in one, recurrent lung collapse and respiratory failure after 10 days in one patient, and the last patient with right ventricular rhabdomyoma who developed heart block and sepsis after 12 days. There was no mortality due to stent occlusions.

Re-interventions

There were three early re-interventions (30%) in the shunt group and included the neonate with technical failure, managed with the ductal stent. Another preterm neonate weighing 1.46 kg after a 3-mm shunt had an early shunt thrombosis. The third infant aged 75 days with transposition of great arteries and pulmonary stenosis had pulmonary over-circulation and was managed by shunt takedown and early conversion to Glenn shunt 2 days later. There was one re-intervention (9%) with aortopulmonary shunt at 3 months following neonatal outflow stent for Fallot's tetralogy for an early recurrence of hypoxia. This child died 12 months later with persistent pulmonary arterial hypoplasia. Six re-interventions (12%) after ductal stents included four shunts through thoracotomy for stenosis of one pulmonary artery due to stent cicatrix and repeat larger ductal stent in two patients. Two of the four surgical shunt re-interventions after ductal stent were performed in the patients who failed initially in their neonatal surgical shunt and immediately rescued with a ductal stent.

Late mortality

Late mortality in 11 patients was seen in 20% after shunts, 18% after outflow stents and 15% after ductal stents. In the shunt group, one sudden-death occurred within 2 months after discharge. The second death occurred 19 months later with progressive cyanosis despite a strong advice to corrective surgery. In the outflow stent group, there were two late deaths. The univentricular patient with tricuspid atresia who underwent outflow stent and documented stent patency at 3-month follow-up died 1 month later at home. An early recurrence of hypoxia in another child at 3 months following neonatal outflow stent for Fallot's tetralogy necessitated an aortopulmonary shunt. This child died 12 months later with persistent pulmonary arterial hypoplasia.

There were seven late deaths (15%) after ductal stents. Three deaths occurred in pulmonary atresia with an intact ventricular septum and a diminutive right ventricle despite a patent ductal stent (Table 4). Death in another patient after pulmonary valvotomy and ductal stent for pulmonary atresia with an intact ventricular septum was due to coexistent mitral regurgitation and pneumonia. Of the three deaths in patients with biventricular

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Table 5. Causes of early hospital mortality and late interval mortality

Cardiac diagnosis	Palliation strategy	Early mortality	Early mortality causes	Late mortality	Late mortality causes
Univentricular lesions other than PAIVS (N = 13)	Surgical shunt (n = 1)	1	Low cardiac output – 1	0	
	RVOT stent (n = 2)	0		1	Sudden death
	Ductal stent (n = 10)	0		0	
PAIVS – without pulmonary valvotomy (N = 8)	Surgical shunt (n = 0)	0		0	
	RVOT stent (n = 0)	0		0	
	Ductal stent (n = 8)	3	Over-circulation – 1 Retroperitoneal bleed – 1 Late sepsis – 1	3	Mitral regurgitation – 1 Pneumonia – 2
PAIVS – with pulmonary valvotomy (N = 12)	Surgical shunt (n = 0)	0		0	
	RVOT stent (n = 0)	0		0	
	Ductal stent (n = 12)	1	Over-circulation – 1	1	Mitral regurgitation – 1
Biventricular lesions (N = 35)	Surgical shunt (n = 9)	1	Low cardiac output – 1	2	Increased cyanosis – 2
	RVOT stent (n = 9)	1	Over-circulation – 1	1	Hypoxia despite shunt – 1
	Ductal stent (n = 17)	4	Low cardiac output – 1 Recurrent atelectasis – 1 Liver abscess, sepsis – 1 Retroperitoneal bleed – 1	3	Increased cyanosis – 2 Hypoplastic arteries – 1
Cardiac rhabdomyoma (N = 1)	Surgical shunt (n = 0)	0		0	
	RVOT stent (n = 0)	0		0	
	Ductal stent (n = 1)	1	Sepsis, heart block–1	0	

PAIVS = pulmonary atresia with intact ventricular septum; RVOT = right ventricular outflow tract

hearts, two occurred at 6 months due to progressive cyanosis and restricted ductal stent flows; both failed to turn up for an additional Blalock–Taussig shunt that was advised at 6-month visit. In the third patient who was 2.1 kg at birth with hypoplastic pulmonary arteries and poor somatic growth, a second drug-eluting stent was deployed within the previous stent after 4 months. The child was followed for another 24 months with slowly progressive cyanosis, but surgical correction could not be completed due to severe pulmonary artery hypoplasia.

Survival till definitive surgery

In the surgical group, there were six survivors (60%) and four of them received the total biventricular correction. Two patients, who had a ductal stent re-intervention, required an additional Blalock–Taussig shunt prior to definitive surgery for left pulmonary artery hypoplasia. One of them was awaiting definitive repair. Following outflow stent, five patients underwent total correction at a median of 9 months (0–15 months) of follow-up. Two patients were awaiting surgical correction after neonatal outflow stent. There were eight survivors (73%) in this group.

Following the ductal stent, there were 31 survivors (65%). Nine patients with univentricular hearts other than pulmonary atresia with intact ventricular septum underwent Glenn shunt at a median of 13 months. Of the two patients with non-confluent pulmonary arteries and bilateral ductal stents, one underwent Glenn shunt at 24 months and the other was alive after 5 years without further surgery due to progressively increasing pulmonary artery pressures, significantly contributed by severe allergic obstructive airway disease despite multiple inhalational agents. Among the patients with biventricular cardiac anatomy, five underwent surgical correction, two underwent an additional Blalock–Taussig shunt, and two underwent re-dilatation of ductal stent due to hypoplasia of pulmonary arteries. Five patients were awaiting surgical correction.

Pulmonary atresia intact ventricular septum

Among 20 patients with this diagnosis, 12 patients had pulmonary valvotomy that provided antegrade flows along with a ductal stent. There was one early death due to pulmonary over-circulation in a neonate with birth asphyxia, despite plugging the ductal stent after 24 hours. One late death after 3 months was due to progressive mitral regurgitation. The 10 survivors had an uneventful course at a median follow-up of 42 months (with a range from 3 to 72 months). In the eight cases with diminutive right ventricle that precluded right ventricular decompression, six died despite documented patency of stent in all patients. Three early deaths were caused by pulmonary over-circulation, retroperitoneal haemorrhage, and late-onset sepsis. The interval deaths in three patients were related to mitral regurgitation in one and pneumonia in two additionally contributed by a large cleft palate in one patient. One patient survived a large intra-cerebral haemorrhage at 13 months with neurological sequelae and was alive at 4 years awaiting a Glenn shunt. Only one case had successful Glenn after 7 months of the ductal stent. There were 12 survivors (60%) in this group.

Duration of palliation

The median time to next surgery in six survivors after shunt was 11 months, shorter in two patients with d-transposition (2 days and 4 months) but longer (11–20 months) in four patients with

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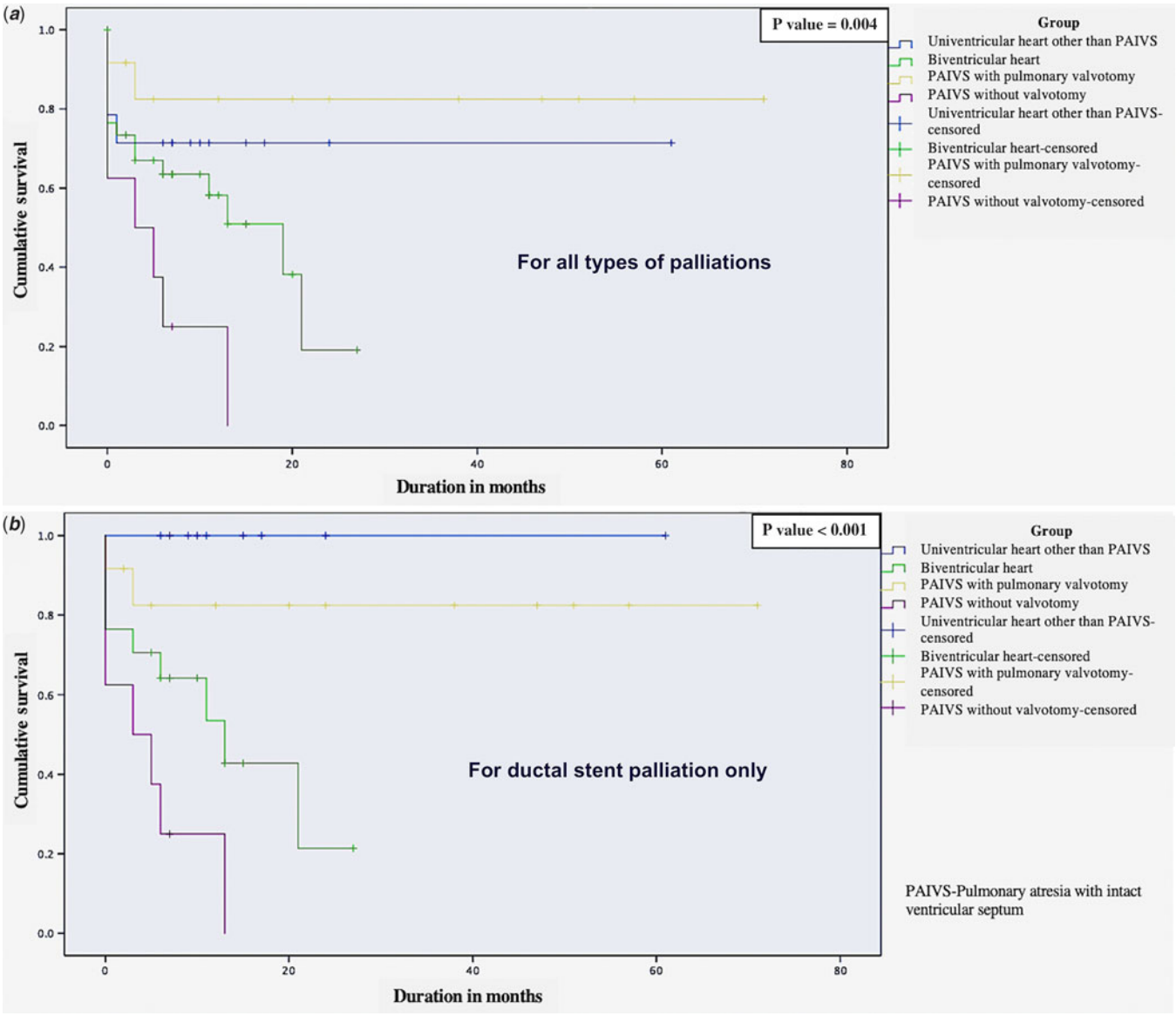

Figure 2. Kaplan–Meier survival plot after any type of palliation (***a***) and after ductal stent (***b***). Survival without any reintervention irrespective of the type of palliation (***a***) is significantly better for pulmonary atresia with the intact ventricular septum (PAIVS), who had pulmonary valvotomy and univentricular hearts other than PAIVS. PAIVS without pulmonary valvotomy had a poor outcome. Survival curve for those who underwent ductal stenting (***b***) also shows a similar outcome (log-rank test).

tetralogy of Fallot. Of the seven survivors after the outflow stent, the median time to next surgery was 11 months (6–15 months) in five children before final correction. Surgery following the ductal stent was performed in 16 patients, (5 biventricular repairs, 2 surgeries in pulmonary atresia intact ventricular septum, and 9 other univentricular hearts) at a median time of 9.5 months (5–27 months) (Table 3). One patient after shunt surgery, two after outflow stent, and seven after ductal stent were awaiting the next surgery.

Comparison of the outcomes between the groups

The late mortality was 16% in our cohort and did not significantly differ between the groups (Table 4). Figure 2 depicted re-interventions-free survival after palliation based on the anatomy. Figure 3 compared the longevity of palliation with the three different strategies. Re-interventions for hypoxia in seven patients (10%) also did not differ between the groups. The pre-hilar pulmonary artery size and symmetry were also similar between all the three groups (Table 3). However, there was a significant increase in the need for pulmonary arterioplasty around the confluence near ductal insertion during the next surgery in the ductal stent group (88%) where the stent caused cicatrisation. The symmetric growth of hilar pulmonary arteries was uniformly noted in all the three groups, as was the pre-surgical Nakata Index (Table 3). As all surgical shunts were performed through sternotomy, asymmetric growth commonly observed after thoracotomy shunts were not observed.[23]

Discussion

Utility of single-institution studies

National Institute for Cardiovascular Outcomes Research, United Kingdom and Society of Thoracic Surgeons Congenital Heart Surgery Database, United States report procedural mortality after

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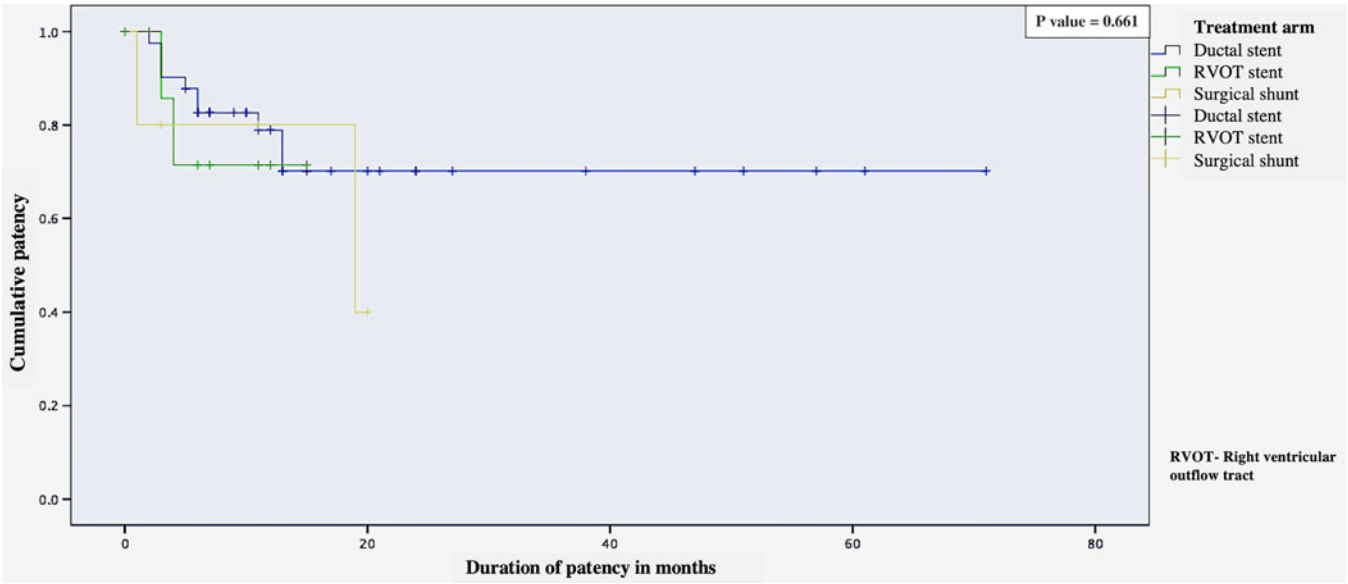

Figure 3. Survival plot for the duration of palliation after successful discharge. There is no significant difference between the types of palliation namely ductal stent, right ventricular outflow tract (RVOT) stent, and surgical shunt (log-rank test).

aortopulmonary shunts varying from 9 to 12% and inter-stage mortality of 6–12%.[3,26] The duration of palliation after shunts or stents vary from 3 to 12 months and institutional protocols decide the timing of corrective surgery.[27] While multi-institutional data take away the institutional bias in the approach, single-centre studies like ours can follow every single patient with an identical protocol and compare between different palliations by reducing the number of management variables typical of a multi-institutional study.[27,28]

Practice patterns differ between institutions

An early Glenn shunt is sometimes performed before 3 months of age to reduce the inter-stage mortality after the initial palliation.[29,30] As this strategy is associated with increased resource utilisation, prolonged ventilation, and intensive care stay, we prefer to do the second stage at 5–6 months of age.[31] Home surveillance monitoring of pulse oximetry, daily weight gain, and recognition of warning signs are suggested to reduce the inter-stage mortality, but they are not always feasible in developing countries.[32] Our institutional preference is to perform univentricular stage II palliations at around 6 months of age and biventricular repair involving placement of right ventricular outflow conduits at 12 months of age. Ductal and outflow stents are preferred in our institution in subsets of patients who are known to be at higher surgical risks such as univentricular hearts, pulmonary atresia with an intact ventricular septum, and hypoplastic pulmonary arteries.[7,22]

Challenges in developing countries

Staged surgeries in low-middle-income countries offer peculiar challenges in resource availability and loss of follow-up.[33] Among the 69 patients in our group, 12 patients had valvotomy and ductal stenting as the destination therapy for pulmonary atresia, intact ventricular septum, and well-developed right ventricle. Barring these patients and one neonate with right ventricular rhabdomyoma, the initial palliation in the rest was expected to maintain clinical stability and survival till the final definitive surgery. Sixty-two percent of these patients survived to the next surgery performed at a median duration of 10 months. In comparison, 77% of 95 patients from Toronto survived after a surgical shunt until the definitive surgery that was performed at a median duration of 5.7 months.[28] Survival was 86% after ductal stents and surgical shunts in 55 patients from Seattle before their next surgery at a median duration of 4.3 and 6.3 months, respectively.[27] Our study observed a longer waiting period and a higher inter-stage attrition. Early biventricular repairs were avoided as they involved more frequent use of transannular patches, more reoperations, and catheter re-interventions.[34] As age and weight were independent predictors for morbidity, total surgical correction was often delayed.[35] Four of the 11 late deaths in our cohort were secondary to progressive mitral regurgitation and pneumonia, while others were due to progressive hypoxia. Despite an advice for surgical shunts to provide additional blood flow for hypoxia, some patients failed to turn up.

Failure to understand the nature of the disease, lack of home monitoring, and economic constraints, which are peculiar challenges in a developing country, could have contributed to some deaths in our cohort. Fewer institutions catering for the treatment of young cyanotic children, non-availability of safe transport for sick patients, longer travel duration to such institutions, lack of universal social security are unaddressed challenges in developing countries.[36] Our institution caters to patients from at least six states from the country. Analysis of poor outcomes in few patients was done by telephonic interviews to ascertain possible causes of mortality in our group. The rarity of clinical autopsies in low-middle-income countries is attributed to ignorance of benefits, religious beliefs, and stigma associated with the procedure.[37]

Alternatives to surgical shunts

Ductal and outflow stenting are explored as alternatives to surgical shunt.[6,7] Despite improved survival, ductal stents in the National multi-centre study required frequent re-interventions before definitive surgery.[7] The in-hospital mortality varied between 9 and 20% and was not different between the three procedures in our group, but this study was not powered to study the difference due to the small number of patients. Many deaths in our study

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were related to non-cardiac causes, namely prematurity, sepsis, recurrent lung atelectasis, birth asphyxia, multi-organ dysfunction, and others, which were known to be associated with poor outcomes in low-middle-income countries.[20,33] The ductal stent was associated with less costs compared to surgical shunt in the Western world.[22] Our group also showed a similar trend as the average hospitalisation costs for surgical shunt, ductal stent, or outflow stent in our centre during the study period were approximately 2500, 1500, and 1600 US dollars, respectively.

Ductal stent as a preferred strategy

After considering the relative experiences with the different palliations, the ductal stent was given Class IIa recommendation by American Heart Association in 2011 in patients with antegrade pulmonary blood flows, but a class IIb recommendation if ducts were the exclusive supply.[38] United States multi-centre study (2012–15) had more patients with antegrade blood flows in the ductal stent arm (61%) compared to 38% in the surgical arm.[6] On the contrary, the ductal stent arm in our study had 79% of patients with exclusive ductal supply compared to 40% in the surgical arm. This reflected a progressive improvement in interventional techniques and experience in the last decade. While ductal stenting in United Kingdom multi-centre data (2012–15) quoted a 16% procedural failure needing a cross over to shunt, our technical success of 100% indicated an evolved learning curve.[7] While comparing different anatomical subsets, our case selection in the study period 2014–2020 showed a preference for catheter interventions in all patients (100%) with pulmonary atresia, intact ventricular septum, and a majority (93%) of patients with other univentricular lesions. Despite a higher surgical risk, previous comparative studies had frequently included these anatomical subsets in the surgical arm.[6,7]

Pulmonary atresia with intact ventricular septum

This disease was associated with high mortality despite palliation with 1 year survival of 70%.[39] When the ductal stent was not concurrently performed, a majority (88%) of infants required shunts following balloon valvotomy.[40] Outcomes after valvotomy and ductal stent were good in our cohort when patients had an adequate right ventricle. Even though 2 out of 12 patients (17%) died after valvotomy either early (due to birth asphyxia) or later (due to progressive mitral regurgitation), the survivors (83%) had a good late outcome, indicating the appropriateness of ductal stent in this setting. But outcomes in patients with diminutive right ventricle were suboptimal despite successful ductal stent and its patency. Low birth weight and severe right ventricular hypoplasia were known risks in this disease, where more than 41% died; 10% achieved univentricular repair, and 17% were left with a mixed circulation in previous studies.[39] A longitudinal analysis of 164 patients in the United Kingdom registry showed that 30% of the patients were dead before the next univentricular surgical repair.[3] Poor outcomes persisted in these patients even during and beyond the second stage of univentricular correction.[41,42] Despite patency of ductal stents, reasons for mortality in our cohort included varied contributions from pneumonia to mitral regurgitation.

Univentricular hearts

Even though univentricular hearts were a known surgical risk for shunts, previous comparative studies included them equally in the ductal stent and surgical arm.[1–3,6,7] Ductal stent offered a gratifying outcome in our patients with univentricular hearts. Glenn shunt was successfully completed in all patients with univentricular hearts, except one with non-confluent pulmonary arteries. There was no procedural or late mortality in univentricular hearts after the ductal stent, indicating the appropriateness of this strategy. A surgical shunt in one patient with tricuspid atresia resulted in early mortality due to persistent hypotension. Outflow stent in two univentricular hearts resulted in one emergent Glenn shunt and one late mortality in our group.

Patients needing biventricular repair

Patients with cardiac anatomy suited for biventricular repair were either referred for surgical shunts, when pulmonary arteries were adequate or outflow stenting, when pulmonary arteries were smaller. Eighty percent of patients referred for surgical shunts and 82% of patients referred for outflow stents had a biventricular cardiac lesion. On the contrary, they accounted for only 38% of infants in the ductal stent arm. A longer duration of palliation provided by surgical shunt was considered as an advantage over ductal stents; however, the median time to definitive surgery in the three groups was similar in this study.[9] A final definitive surgical correction was achieved in 45% of the patients after any palliation and 18% were awaiting surgery. There were no significant differences between the three groups. Intensive home monitoring by pulse oximetry, parental education, strict compliance about close follow-up, aggressive re-interventions for hypoxemia, and organising financial assistances are likely to improve the number of patients who achieve definitive repair.[32]

Limitations

The study has the limitations inherent in any retrospective analysis. Choice of palliation was dependent on multiple factors that not only included the anatomy of the lesion and the comorbidities, but also occasionally on cost differences between the procedures inherent to developing countries and hence sometimes might not be considered as the "objective best choice". Telephonic contacts were established to ascertain inter-stage mortality. Even though in-hospital deaths could be investigated with echocardiogram for patency of shunt or stent, no autopsy was performed to ascertain the causes of late deaths. Illiteracy, restricted resources, parental apathy, inter-current illnesses, and non-compliance with drugs might have played a role in the suboptimal follow-up and poor outcomes and these were the inherent problems of low-middle-income economies.

Conclusions

The outcome of very young cyanotic patients in developing countries weighing less than 5 kg with critically reduced pulmonary blood flow was suboptimal. Outcomes and re-interventions were similar regardless of the type of palliation. The technical success of 100% with ductal stents did not translate to better long-term outcomes. Good outcomes in pulmonary atresia with intact ventricular septum after balloon valvotomy and other univentricular lesions indicated the appropriateness of ductal stents in these subsets. Outcomes were extremely poor in pulmonary atresia with an intact ventricular septum and diminutive right ventricle, despite patency of the ductal stents due to various other reasons. Many patients with biventricular lesions did not reach corrective surgery due to a combination of anatomical and extraneous factors. Parent

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education, home monitoring, financial assistance, and family support may improve outcomes in these patients.

Clinical perspective

Aortopulmonary shunts that palliate cyanotic young infants are associated with measurable mortality, especially in univentricular hearts and pulmonary atresia with an intact ventricular septum.

Ductal stents and right ventricular outflow tract stents are emerging alternative options with comparable outcomes.

Despite advances in surgery and interventions, wide disparities exist in resource-restricted nations that face unique challenges with compliance, follow-up, and inter-stage mortality.

Parent education, home monitoring, and family support might improve outcomes.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Indian council of medical research and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee of Madras Medical Mission, Chennai, India.

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