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What are the non-cardiac prognostic factors affecting mortality in neonates with aortopulmonary shunt

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ABSTRACT

Background/aim: Systemic to pulmonary shunts (SPS) have proven to be highly effective for the palliation of neonates with cyanotic congenital heart disease. Mortality after SPS surgery in neonates has multifactorial basis. We aimed to investigate the clinical results of the SPS in relation to the underlying cardiac disease and to identify the risk factors contributing to an adverse outcome.

Material and method: All neonates who underwent first shunt insertion for cyanotic congenital heart disease during the study period from 1 January 2014 to 31 December 2017 were included. A retrospective review of patient records was done. Patients were grouped into two different categories: survived with or without any reintervention and death before or after any reintervention till discharge.

Result: During the study period, 47 patients underwent SPS shunt placement. Patients who survived with or without any reintervention were in Group 1 and patients who died before or after any reintervention till discharge were in Group 2. Preoperative epinephrine requirement and mechanical ventilation and postoperative erythrocyte transfusion need were statistically significant.

Conclusion: Although primary cardiac pathology is the most important prognostic factor, some other preoperative and postoperative factors like preoperative epinephrine requirement, and postoperative erythrocyte transfusion might also affect the prognosis. As there are very few centers in the region that specialize in pediatric cardiac surgery, a multicenter approach will be helpful in reaching reliable conclusions.

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Introduction

The incidence of congenital heart disease (CHD) has been estimated to be 6–8/1000 live births in the general population [1–3]. Infant's death from CHD accounts for around 3% [4]. Systemic to pulmonary shunts (SPS) have proven to be highly effective for the palliation of neonates with cyanotic congenital heart disease who are not candidates for early complete repair. Palliation through the creation of systemic–pulmonary shunts is commonly done to achieve vital stability and to buy time untill corrective surgery or heart transplantation. According to a recent harvest report of the Society of Thoracic Surgeons Congenital Heart Surgery Database, mortality for a neonatal modified Blalock–Taussig shunt was 7.1% [5]. Mortality after SPS surgery in neonates has multifactorial basis. The most important fact is that the patient population is extremely vulnerable at baseline due to young age, hemodynamic compromise and immature immune system. Anastomosing the shunt closer to the PA bifurcation, allowing even distribution of blood to both lungs, is highly desirable [6,7].

In this retrospective study, we aimed to investigate the clinical results of the SPS in relation to the underlying cardiac disease and to identify the risk factors contributing to an adverse outcome.

Materials and methods

All neonates who underwent first shunt insertion for cyanotic congenital heart disease during the study period from 1 January 2014 to 31 December 2017 were included. A retrospective review of 47 patient records was done. Patient information was obtained from the medical records of all patients who underwent SPS. A 3–3.5 mm polytetrafluoroethylene

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(Gore-Tex; WL Gore and Associates, Inc, Newark, DE) graft was used at our institution. We had 3.5 mm graft only but this graft is narrowed with a clip in infants less than 3 kg.

All patients were characterized by gender, gestational age, birth weight, inborn or outborn, presence of significant non-cardiac congenital abnormalities (including identified genetic syndromes), and presence of heterotaxy syndrome, underlying cardiac diagnosis, and age at SPS shunt placement. Cardiac diagnoses were obtained by the review of echocardiogram, cardiac catheterization, and operative reports. Patients were grouped into two different categories: survived with or without any reintervention and death before or after any reintervention till discharge. Primary cardiac pathologies are grouped according to univentricular (UV) or biventricular (BV) physiology.

The age at operation, cardiac pathology (UV or BV), antenatal diagnosis of cardiac defects, preoperative inotropic agent requirement, cardiac arrest both intraoperative and postoperatively, sepsis both during last week before operation and in postoperative first week, preoperative serum albumin level and serum lactate level 48 h before and 72 h after the operation, thrombocytopenia after operation in 6 h, postoperative inotropic requirement were recorded.

The patients received prostaglandin E1 infusion before the operation if indicated and underwent primary central shunt placement through a median sternotomy approach according to the method reported by Gates and colleagues [7] without the use of cardiopulmonary bypass. Two surgeons did the operations during the study period. Although the most common approach for SPA shunt has been the thoracotomy incision, we preferred median sternotomy and central shunt.

Dopamine infusion at a dose of 5–10 g/kg per minute was administered as the first line inotropic agent in all patients. Target mean pressure was 40–45 mmHg and systolic pressure was 55–75 mmHg. Epinephrine infusion was added according to the clinical situation as the second line inotropic agent. Milrinone infusion at a dose of 0.5–1 mg/kg/min was administered after epinephrine and then dexamethasone or norepinephrine was added if needed to support blood pressure according to serum cortisol levels. Fraction of inspired oxygen depended on arterial saturations, with target values of 75–85%. The sternum was closed in the standard fashion.

All patients were mechanically ventilated and received continuous infusions of morphine for a minimum of 3 d until the closure of sternum postoperatively. Postoperatively, heparin was administered as a continuous infusion at 10–20 units/kg/h with conversion to aspirin after 24 h once enteral tolerance was achieved. We also recorded the volume of RBC transfusions in ml per kg (ml/kg) during the operation and daily for the first 3 d after.

The indications for RBC transfusion in these patients include: (i) hematocrit $<35\%$, (ii) continued bleeding, and/or (iii) evidence of decreased oxygen-carrying capacity, for example, demonstrated by a low mixed venous saturation and/or tachycardia. We consider postoperative bleeding to be significant if blood loss exceeds 10 or 4 ml/kg/h for three consecutive hours.

Primary outcomes measures included mortality, defined as death occurring any time after the shunt procedure and before discharge.

Neonates with complete transposition who underwent SPS and pulmonary artery banding as part of a rapid two-stage arterial switch and all neonates with hypoplastic left heart syndrome that were eventually treated with the Norwood procedure were excluded.

The study was approved by the Ethical review committee of the hospital. No information about patient identity was recorded.

Statistical analysis

The data were analyzed using SPSS 19.0 software package for Windows (SPSS, Chicago, IL). Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as mean and standard deviation (median and minimum–maximum if necessary). Chi-square test was used to compare groups for categorical variables and continuous variables were compared using the *t*-test for normally distributed variables. The Mann–Whitney *U* test was used for non-normal distributed continuous data. *p* Values less or equal to .05 were accepted as statistically significant.

Results

During the study period, 47 patients underwent SPS shunt placement at a median 20.2 d of age (1–117 d); 51.6% (24/47) were male. Prognostic factors were shown in Table 1(a) and (b). Mean birth weight was 2794 ± 599 (1420–3900) g, and 23.4% (11/47) had a birth weight (BW) less than 2.5 kg; 19.1% (9/47) were premature. Twenty-eight patients had UV physiology and 19 patients had BV physiology. Twelve patients with ventricular septal defect + pulmonary atresia, three patients with Fallot tetralogy and four patients

Table 1. Compared prognostic factors between groups.

(a)	Group 1 ($N = 31$) Mean ± SD (min–max) median	Group 2 ($N = 16$) mean ± SD (min–max) median	p
Preop Htc %	42.95 ± 7.83 29.20–63.90 42	42.60 ± 6.59 31.00–55.00 43.7	.893
Operation age (day)	19.1 ± 14.9 1–57 13.5	20.12 ± 26.92 4–117 13	.551
Postop MV duration (day)	6.87 ± 6.07 2–26 5.0	10.2 ± 14.94 1–61 5.5	.821

(b)	Group 1 ($N = 31$) n (%)	Group 2 ($N = 16$) n (%)	p
BW < 2500 g	**4 (19.9)**	**7 (43.8)**	**.029**
GW ≤ 37 weeks	6 (19.3)	6 (37.5)	.174
Male	19 (61.2)	5 (31.3)	.069
Antenatal diagnosis+	9 (29)	4 (25)	.999
Primary UV physiology ($n = 28$)	16 (57.1)	12 (42.8)	.108
Primary BV physiology ($n = 19$)	15 (78.9)	4 (21.1)	
Preop sepsis+	6 (19.3)	3 (18.7)	.999
Preop Albumin <2.5 g/dl	4 (12.9)	2 (12.5)	.999
Preop dopamine inf+	2 (6.4)	2 (12.5)	.597
Preop epinephrine inf+	**0 (0)**	**3 (18.7)**	**.035**
Preop MV	9 (29)	**6 (37.5)**	**.019**
Intraoperative cardiac arrest (+)	2 (6.45)	0 (0)	.541
Postop cardiac arrest+	**4 (12.9)**	**8 (50)**	**.012**
Postop RBC transf > 60 ml/kg in first 3 d	**12 (38.7)**	**15 (93.8)**	**<.001**
Postop sepsis+	11 (35.4)	8 (50)	.366
Postop thrombocytopenia+	9 (29.3)	7 (43.7)	.347
Postop Lactate > 2.5 mEq/l	**11 (35.4)**	**11 (68.8)**	**.037**
Postop epinephrine inf+	26 (83.8)	16 (100)	.150
Postop norepinephrine inf+	13 (41.9)	11 (68.7)	.125
Postop DXM inf+	15 (48.3)	10 (62.5)	.538
Shunt occlusion	3 (9.5)	2 (12.5)	.999

Preop: preoperative; postop: postoperative; MV: mechanical ventilation; GW: gestational week; inf: infusion; preop: preoperative; postop: postoperative; MV: mechanical ventilation; DXM: dexamethasone.
p values < .05 were accepted as significant and bold in the table.

with transposition of great arteries + pulmonary stenosis had biventricular physiology (BV) while six patients with intact ventricular septum + pulmonary atresia, five patients with tricuspid atresia, four patients with double outlet right ventricle + left ventricle hypoplasia, five patients with heterotaxy syndromes, and eight patients with other cardiac pathologies had univentricular physiology. Hospital mortality occurred in 16 (34%) patients; 12/16 (75%) in the UV physiology and 4/16 (25%) in the BV physiology. Of 28 patients, 12 (42.8%) patients of primary UV physiology and 4/19 (21.1%) patients with primary BV physiology died ($p = .108$, Table 1(b)). Three patients had significant AV valve regurgitation and two of them (with Ebstein anomaly and tricuspid valve dysplasia). Five patients with heterotaxy syndrome died. Patients were grouped into two different categories: survived with or without any reintervention (group 1) and death before or after any reintervention till discharge (group 2). Mean birth weight and gestational week were 2911.93 ± 553.75 (1420–3900) g and 38.30 ± −2.49 (32–41) weeks in group 1 and 2563.75 ± 633.11 (1760–3560) g and 37.68 ± 2.60 (32–40) weeks in group 2, respectively ($p > .05$).

Only 15 infants were inborn (31.2%). One patient was transported to our unit at 107 d of age and operated at the 117th day of life. One patient had anal atresia, one had diaphragmatic hernia, and one had tracheoesophageal atresia in addition to cardiac defects. None of the patients had trisomy or 22q deletion.

About 37.5% (6/16) of patients in group 2 died within 24 h after the operation, 25% (4/16) died 3 d after the operation due to cardiac causes, while 37.5% (6/16) died 15 d after the operation due to cardiac and non-cardiac causes (sepsis, ARDS, arrhythmias, necrotizing enterocolitis, etc.).

Patients (11/47, 23.4%) with a birth weight <2500 g had 3 mm shunt while others had 3–3.5 mm shunt. Five patients, three from group 1 and two from group 2, had shunt occlusion and required reintervention.

Discussion

The systemic-to-pulmonary shunt is widely used in the surgical palliation of various forms of CHD. Despite

improvements in operative mortality in recent decades that parallel increased survival in children with CHD, patients with shunt-dependent pulmonary blood flow continue to experience significant early and late mortality. With early intervention, neonatal mortality from the heart can fall from 2–3/1000 to 0.6–0.8/1000 live births [2,4]. The systemic-to-pulmonary artery shunt is associated with significant mortality and morbidity. The mortalities are 9% in the study of Alsoufi et al. [8] and 13.6% in the report of Ahmad et al. [9]. Moreover, the risk factors for mortality and reintervention in this specific population are still controversial. Our mortality rate was 34%.

The high-risk groups include patients with low weight, prematurity, single ventricle physiology, pulmonary atresia and intact ventricular septum, heterotaxy syndromes, genetic syndromes, and extra cardiac malformations.

Petrucci et al. [10] reported a discharge survival rate as 89% in patients weighing less than 3 kg. Another report by Erez et al. [11] evaluated outcomes using saphenous vein homografts as shunts in patients weighing less than 3 kg. In that series of 32 patients, hospital survival was approximately 94%, but overall survival was approximately 80%.

Although Seo et al. [12] found that lower weight at the time of surgery was not associated with mortality, low birth weight is still considered an important risk factor for heart surgery [13]. In our study, there was more infants having birth weight $<$2500 g in group 2 and this was statistically significant ($p = .029$). The high-risk groups include patients with low weight, prematurity, single ventricle physiology, pulmonary atresia and intact ventricular septum, heterotaxy syndromes, genetic syndromes, and extracardiac malformations.

Cardiac pathology is a very important factor for prognosis. It is worth noting that the consequences of shunt over circulation are more profound in univentricular physiologies, patients with complete AV canal, pulmonary atresia with an intact septum to coronary arteries sinusoids, all of which are ill-served in different ways by excessive Qp:Qs. Increased AV valve regurgitation leads to increased coronary steal and low systemic output. In our study, hospital mortality occurred in 16 (34%) patients; 12/16 (75%) in the UV physiology and 4/16 (25%) in the BV physiology ($p > .05$), and two out of three patients having clinically AV regurgitation died.

Developing countries suffer from a greater burden of infectious diseases which affect survival rates after complex surgeries by increasing postoperative morbidity and mortality through sepsis [9]. Sepsis of pulmonary or intestinal origin might cause a progressive imbalance of both systemic and pulmonary circulations. Also, sepsis might increase the inotropic requirement of the patients. In our study, neither preoperative sepsis nor postoperative sepsis were significantly different between the two groups ($p = .99$ and $p = .36$).

Myers et al. [5] reported that outcomes were good with the 3.5 and 4 mm shunts; however, shunt reintervention was common with 3-mm shunts. In our study, all the patients had 3–3.5 mm shunt. Still, 5 patients had shunt occlusion and needed reintervention (three of them had 3 mm shunt graft). Increased shunt size to weight ratio was a significant risk factor for mortality. Alsoufi et al. [8] titrated the shunt size to around 1.16 (0.9–1.6) mm/kg body weight. The general rule of thumb is to select a shunt size of 3 mm for body weight up to 3 kg and 3.5 mm for body weight around 3.5 kg.

Engelman et al. [14] compared mortality and morbidity after cardiac operations and they reported that low albumin level ($<$2.5 g/dl) was associated with increased mortality after cardiopulmonary bypass. In addition to this report, Bhamidipati et al. [15] also examined patients who underwent coronary bypass surgery to determine complications and mortality at different preoperative serum albumin levels. They found that albumin $<$2.0 g/dl increased the likelihood of major complications and higher albumin levels reduced the rate of death within 30 d after surgery. In our study, preoperative albumin levels were not different between groups.

The maintenance of appropriate hemodynamic goals is essential to improve outcomes after cardiac surgery. Perfusion markers such as central venous oxygen saturation and blood lactate may, therefore, represent important tools for the management of these patients [16].

Hyperlactatemia is common after cardiac surgery and is associated with poor outcomes [17–21]. It mainly appears to be related to an unbalance between oxygen delivery and requirement during cardiopulmonary bypass or after cardiac surgery. Lactate production increases in cells as a result of anaerobic glycolysis. In our study, a number of patients with postoperative lactate level $>$2.5 were significantly higher in group 2. This study has demonstrated that lactate levels at the end of cardiac surgery, immediately after NICU admission and also at 6 h later, are related to postoperative adverse events.

Zahorec et al. [22] reported that in newborns with pulmonary atresia, ductal closure during SPS shunt is

associated with an increased incidence of resuscitation, and increased mortality during the early postoperative period. In our study, all the patients had ductal closure during operation so that this parameter was not compared between groups.

A multicenter study from America and Europe including 1000 children demonstrated a shunt blockage rate of 12% [23]. In our study, the shunt blockage rate was only 10.6% (5/47 patients). Gedicke et al. reported that the main risk factors for blockage of shunts that might have a role in prognosis were preoperative high hemoglobin levels [24]. In our study, preoperative hematocrit levels were not different between groups.

In studies with adult and pediatric patients, RBC transfusions have been shown to be independently associated with increased morbidity and mortality [25–27]. Some of the complications associated with RBC transfusion include infections, electrolyte abnormalities, circulatory overload, allergic reactions, and transfusion-related acute lung injury [28]. The number of patients requiring >60 ml/kg postoperatively in the first 3 d of life is statistically significant. Bleeding is one of the major complications of SPS operations. In our study, patients required erythrocyte transfusion for both oxygenation or to compensate bleeding is significantly more in group 2.

Our study is subject to the limitations and biases inherent to a retrospective single-institutional study of a small cohort. The power of our study was, however, too small to enable any strong statements to be made. Future multicenter, randomized controlled trials are needed to investigate this topic in further detail. As there are very few centers in the region that specialize in pediatric cardiac surgery, a multicenter approach will be helpful in reaching reliable conclusions.

In conclusion, the significant management of systemic pulmonary shunt in neonates presenting with severely reduced pulmonary blood flow remains controversial.

Disclosure statement

No potential conflict of interest was reported by the authors.

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