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ORIGINAL ARTICLE

Dismal Outcomes of Second-Run Extracorporeal Life Support in the Paediatric Population

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Background In 2011 we reported unfavourable outcomes of second-run extracorporeal life support (ECLS) in children. We wanted to investigate whether this previous report affected our strategy and modified our long-term outcomes.

Methods Between 1988 and 2015, 31 patients underwent a second-run ECLS. Median age at the time of first support was 9 days (0–16 years). Median length of support for the first and second runs were 4.7 days (0.1–10) and 3.6 days (0.5–8.7) respectively, with an interval of 1.8 days (0.1–66) between supports.

Results There was an increasing trend in the number of patients undergoing second-run ECLS after our report: 21 patients between 1988 and mid-2010 (0.9 patients/year) and 10 between mid-2010 and 2015 (two patients/year) ($p = 0.06$). However, among all the patients who underwent ECLS, the proportion of second-run ECLS was not different before and after 2010 (4% vs. 4.2% respectively, $p = 0.92$). While 58% of patients (18/31) survived weaning of support, only 23% (7/31) survived to hospital discharge and 14% (5/31) were still alive after hospital discharge at a median of 6.5 years (1.2–11.6). The three patients who had positive long-term outcomes had the second-run ECLS instituted to allow for major cardiac operations.

Conclusions Compassionate use of second-run ECLS is difficult to refuse but one should be aware that its outcomes are dismal. In our centre, benefits seem to be limited to cases where the second-run ECLS allows for a major cardiac intervention.

Keywords Circulatory temporary support • Congenital heart disease • Extracorporeal membrane oxygenation

Introduction

There are only scarce reports of outcomes of repeat extracorporeal life support (ECLS) in children [1–5]. The immediate outcomes are known to be unfavourable but the mid-term results are uncertain. In 2011, we reviewed the data of all children who underwent a second-run ECLS in our department since the introduction of the ECLS program in 1988 [6]: 15% of patients were alive after hospital discharge at a median follow-up of 42 months. Given these dreary outcomes, we suggested avoiding such a strategy.

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After an internal audit, it has been noted that a number of patients were still undergoing a second-run ECLS recently in our centre despite our own recommendation. Accordingly, we decided to review our data to investigate whether we effectively changed our practice and to report the current outcomes of our patients undergoing a second-run ECLS to identify the patients who could benefit from a repeat support.

Patients and Methods

The design of the study was approved by the Royal Children's Hospital Human Research Ethics Committee, and the need for consent was waived. All patients who underwent a second-run ECLS, extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD), during the same hospital stay were included in the study. An arbitrary period of 3 hours was defined as a minimal interval between the first and second-run ECLS to consider the event as a second-run rather than the same ECMO episode. Patients who had a long-term VAD were excluded from the study.

The records of all consecutive children who underwent a second-run ECLS from September 2010 to December 2015 were reviewed. The data of the patients from the previous report, supported from May 1988 to August 2010, were added to the current study.

Statistical Analysis

Data are reported as median (range) or mean +/− standard error of the mean as appropriate. Continuous outcomes were compared using the Mann-Whitney test. Differences in proportions were tested using the Pearson chi-square test or the Fisher's exact test when appropriate. Analyses were performed with IBM SPSS Statistics 21.0 (IBM, Armonk, USA).

Results

Overall Picture of the ECLS Program at the Royal Children's Hospital From 1988 to 2015

Over 28 years, between May 1988 and December 2015, 757 patients underwent 902 runs of ECLS at our institution. There were 709 ECMO runs (78.6%) and 193 VAD runs (21.4%).

Among the 757 patients, 571 patients (75%) underwent an ECMO support only (single or multiple runs), 121 patients (16%) underwent a VAD support only (single or multiple runs) and 65 patients (9%) underwent an ECMO preceded or followed by a VAD support.

Interestingly, the mean frequency of ECLS runs increased dramatically after 2010 (Figure 1): 27.0 ± 2.6 runs/year from May 1988 to August 2010 (Period 1) versus 56.5 ± 2.0 runs/year from September 2010 to December 2015 (Period 2) ($p < 0.001$). The same observation was made for the number of patients supported each year: 23.2 ± 2.0 patients/year over Period 1 versus 44.3 ± 1.6 patients/year over Period 2 ($p < 0.001$).

Patients Undergoing a Second-Run ECLS

Thirty-one patients underwent a second-run ECLS over 28 years in our institution: 21 patients from May 1988 to August 2010 and 10 patients from September 2010 to December 2015. Patients' characteristics and indications are given in Table 1.

The number of patients who had at least two runs of ECLS increased in absolute value: 0.9 ± 0.2 patients/year underwent a second-run ECLS over Period 1 versus 2.0 ± 0.4 patients/year over Period 2 ($p = 0.06$). However, there was no difference in proportions: among all the patients who underwent an ECLS run, 4% (21/519 patients) underwent

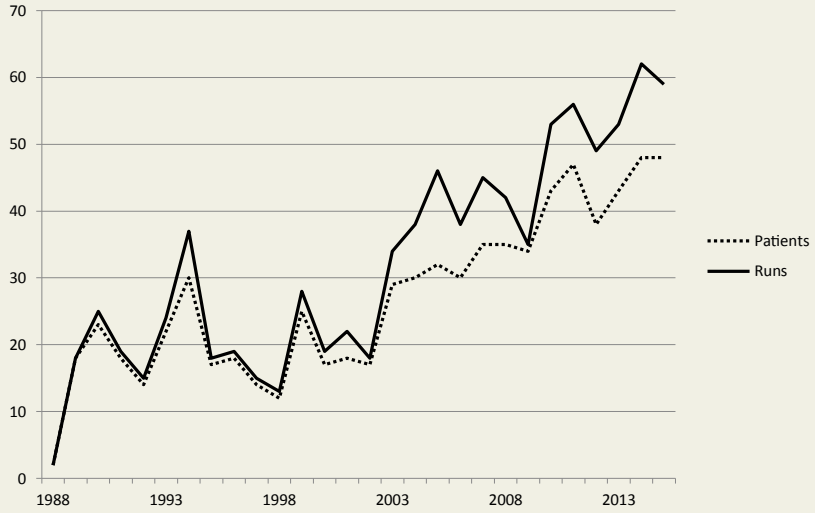

Figure 1 Graphs showing an increasing ECLS activity in our institution from 1988 to 2015.

a second-run ECLS during Period 1 versus 4.2% (10/238 patients) during Period 2 (p = 0.92). In our group of children who underwent ECLS support, a total of 4.1% (31/757 patients) underwent a second-run ECLS as previously defined.

Cardiac patients represented 81% of the cohort (25/31 patients) and non cardiac patients 19% (6/31 patients) (Table 2).

Outcomes

Median age at the time of first support was 9 days (0–16 years). Median length of support for the first and second runs were 4.7 days (0.1–10) and 3.6 days (0.5–8.7) respectively, with an interval of 1.8 days (0.1–66) between supports.

Fifty-eight (58%) per cent of patients (18/31) survived the second-run ECLS. There was no difference between Period 1 and Period 2 (Table 2). However, only 23% (7/31 patients) survived to hospital discharge, without any noticeable difference between the two periods. After a median follow-up of 6.5 years (1.2–11.6), five patients (14%) were still alive. Survival during Period 1 and 2 was respectively 12% and 20%. Two of these five long-term survivors have severe neurological deficits. All three patients who had a positive long-term outcome had ECLS instituted before or after the following major cardiac operations: bidirectional cavopulmonary connection (BCPC) after repair of Ebstein's anomaly, BCPC takedown and central shunting, and arterial switch operation (Table 3).

Table 1 Patients' characteristics.

	Results, n = 31	
Male	14 (45%)	
Mean age at the time of first ECLS run	9 days (0–16 years)	
Diagnosis		**Survival**
Cardiac	25 (81%)	5/25 (20%)
Univentricular hearts	13 (42%)	2/13 (15%)
• HLHS: 6/HRV: 3		
• Unbalanced AVSD: 2		
• Shone's complex: 1		
• PA/intact ventricular septum: 1		
Biventricular hearts	8 (26%)	2/8 (25%)
• AVSD/tetralogy of Fallot: 1		
• VSD/coarctation: 1		
• Aortic stenosis/hypoplastic arch: 1		
• Ebstein's anomaly: 2		
• PA/VSD/MAPCAs: 1		
• TAPVD: 1		
• Transposition of the great arteries: 1		
Cardiomyopathy and equivalents	4 (13%)	1/4 (25%)
Non cardiac	6 (19%)	0/6 (0%)
• Sepsis:1/Pneumonia:1		
• Congenital diaphragmatic hernia: 1		
• Biliary atresia (liver transplant): 1		
• Tracheal stenosis: 2		
Types of ECLS for the 2 runs		
ECMO only	24 (77%)	
ECMO and VAD	7 (23%)	
Indications of ECLS	**First run**	**Second run**
Low cardiac output	20 (64.5%)	15 (48.4%)
Cardiac arrest*	2 (6.4%)	9 (29.1%)
Hypoxaemia	4 (12.9%)	2 (6.4%)
Pulmonary hypertension	3 (9.7%)	3 (9.7%)
Respiratory support for tracheal procedure	2 (6.4%)	2 (6.4%)

Abbreviations: HLHS, hypoplastic left heart syndrome; HRV, hypoplastic right ventricle; AVSD, atrioventricular septal defect; PA, pulmonary atresia; VSD, ventricular septal defect; MAPCA, major aortopulmonary collateral artery; TAPVD, total anomalous pulmonary venous drainage.

*p = 0.02 for the comparison between the first run and the second run.

Table 2 Outcomes of Second-Run Paediatric Extracorporeal Life Support (ECLS) at our Institution.

	Period 1 May 1988 to August 2010	Period 2 September 2010 to December 2015	Overall May 1988 to December 2015
Number of patients	21 (16 cardiac, 5 non cardiac) 0.9 patients/year 4% of all ECLS (25/519 patients)	10 (9 cardiac, 1 non cardiac) 2 patients/year 4.2% of all ECLS (10/238 patients)	31 (25 cardiac, 6 non cardiac) 1.2 patients/year 4.1% of all ECLS (31/757 patients)
Survival to second run*	12 (57%) 8/16 cardiac, 4/5 non cardiac	6 (60%) 5/9 cardiac, 1/1 non cardiac	18 (58%) 13/25 cardiac, 5/6 non cardiac
Survival to discharge*	5 (24%) 3/16 cardiac, 2/5 non cardiac	2 (20%) 2/9 cardiac, 0/1 non cardiac	7 (23%) 5/25 cardiac, 2/6 non cardiac
Currently alive*	3 (12%) 3/16 cardiac, 0/5 non cardiac	2 (20%) 2/9 cardiac, 0/1 non cardiac	5 (14%) 5/25 cardiac, 0/6 non cardiac

*p = 1 for the comparison between Period 1 and Period 2.

Table 3 Course of the 3 patients who underwent a second-run ECLS with favourable outcomes.

Patients	Diagnosis	Cardiac operation	First-run ECLS duration	Cardiac operation	Second-run ECLS duration	Cardiac operation
1	Ebstein's anomaly	1/Tricuspid valve repair	1.8 days	N/A	3.6 days	2/BCPC
2	Mitral stenosis Double outlet right ventricle PDA	1/PDA ligation 2/BCPC MPA banding MPA division Atrial septectomy	3.5 days	3/BCPC revision Right pulmonary artery enlargement	5.3 days	4/BCPC takedown Central shunting
3	Transposition of the great arteries	N/A	1.8 days	1/Arterial switch operation	2.3 days	N/A

Abbreviations: PDA, patent ductus arteriosus; MPA, main pulmonary artery; BCPC, bilateral cavopulmonary connection; N/A, not applicable; ECLS, extracorporeal life support

Third-Run ECLS

Six patients who underwent a second-run ECLS had a third run. Five patients were cardiac and one patient was non cardiac (pulmonary hypertension). The median duration of the third mechanical support was 3.7 days (0.5–5.9) after a median interval with the second run of 15.4 days (1.35–92.1). None of these six patients survived the third-run ECLS.

Discussion

It is known that the outcomes of second-run ECLS are characterised by an increased morbidity and mortality when compared to single-run ECLS, for which survival rates are reported at around 50% in the paediatric population [7–10]. We found similar results in our 2011 report. In the current study, we confirm the dismal outcomes of patients who undergo a second-run ECLS: of the 31 patients, only five (14%) were still alive after a median follow-up of 6.5 years. However, two patients out of five died after discharge during the early period, whereas the two patients who were discharged in the recent era are still alive with no significant morbidity.

To our knowledge, we report the largest cohort of paediatric patients who underwent a second-run ECLS in a single institution. Our survival-to-discharge of 23% is equivalent to the one reported by Shuhaiber et al. [4], whose population was similar to ours with a large proportion of patients supported for cardiac indications. It is interesting to note that our results are also comparable to the ones reported by Gupta et al. [11] who found a survival to hospital discharge and overall survival rate of 19% and 14% respectively in patients undergoing a single but long run ECMO (≥28 days). Both practices likely identify poorer candidates for support.

We do believe that our poor results with second-run ECMO stems from the selection of poor candidates for repeated support rather than premature weaning of our patients. Our centre has historically been one of the first to

adopt ECMO technology and we are only weaning ECMO when we are certain to have given an appropriate length of support. Our ECMO length of support was very similar to those previously published by others [4]. A majority of our patients who died had a lack of recovery of myocardial function. Once supported, it becomes extremely difficult to estimate accurately this recovery. Currently, before weaning definitely, we decrease the flow to the lowest acceptable level (around 150 mL/min) with administration of a small amount of inotropic support and echo monitoring. But the validity of this testing remains doubtful and clinicians are still left to their clinical good sense to make the difficult decision of the best time for weaning.

In 2011, after the publication of our previous manuscript, we internally recommended to refuse second-run ECLS in our patients. Despite this intention, our rate of second-run ECLS did not vary. Our experience is once again demonstrating the lack of power of published evidence in influencing decision-making in our practice in the setting of life threatening situations. The failure of our community to stick to guidelines has already been extensively reported [12,13]. It has been our policy to initiate mechanical support, not only as a bridge to diagnosis, a bridge to another procedure or to recovery, but also to allow families to come to terms with the loss of their child. While the proportion of this latter indication is difficult to ascertain retrospectively, one would certainly agree that elective withdrawal of care under ECLS is easier to accept for the team and the families than an acute unexpected event. In this perspective, it is likely that second-run ECLS will remain in use in our institution. Even though we could not demonstrate any major differences in survival between the two periods, there was a slight improvement in overall survival (20% vs. 12%) and it is possible that we have been slightly more selective in our indications for repeated support.

We have in our institution a rapid ECMO deployment policy for all paediatric patients with cardiac disease undergoing a cardiac arrest or a near arrest event. Our current policy is that, once the call is made, there is no longer any discussion about indication until the patient is under support. Because this policy led us to futile support of some patients, such as those supported with second-run and third-run ECMO, all patients in ICU are now discussed and flagged to be either candidate or not candidate for ECMO. This status is recorded in the chart of the patient. We will, in a few years, be in a position to evaluate the efficiency of this practice.

From our experience, the patients who benefit from a second-run ECLS are the ones with the most favourable cardiac anatomy, such as Ebstein's anomaly and transposition of the great arteries. Some categories of patients seemed to have very few chances of any benefits in our hands. Only one of the six patients with a diagnosis of hypoplastic left heart syndrome is currently alive, with a major neurologic impairment. In addition, none of the patients from the non cardiac group survived.

As a conclusion, the global outcomes of second-run ECLS have not improved in the recent period. Compassionate use of second-run ECLS is difficult to refuse but one should be aware that its outcomes are dismal. However, our experience now suggests that patients can be better selected according to their cardiac anatomy.

Acknowledgements and Disclosure

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Conflict of Interest

Yves d'Udekem is a consultant for MSD and Actelion. Christian P Brizard is a member of the Advisory Board to Admedus Australia.

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