Original Article

Neonatal and Paediatric Extracorporeal Membrane Oxygenation (ECMO) in a Single Asian Tertiary Centre

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Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique (CPB) which provides life-saving support in patients with refractory cardiorespiratory failure until cardiopulmonary recovery or organ replacement. Materials and Methods: This is a single centre retrospective study reporting the largest series of paediatric patients in Singapore who received ECMO support over an 11-year period from January 2002 to December 2012. The objective is to describe the characteristics of the patients and to report the survival to hospital discharge, complications during ECMO and other long-term complications. Results: Forty-eight patients received ECMO during the study period. ECMO was initiated for myocarditis in majority of the paediatric patients whereas postoperative low cardiac output state was the most common indication in the neonatal population. The overall survival rate to hospital discharge was 45.8%. Survival was highest in the neonates with respiratory failure (75%). Haematological and cardiac complications were most common during ECMO. Age group, gender, duration of ECMO, need for renal replacement therapy, acute neurological complications were not associated with mortality. Those needing inotropic support during ECMO had poorer survival while those with hypertension requiring vasodilator treatment had a higher survival rate. The survival rates for ECMO patients more than doubled from the initial 6 years of 23% to 54% in the last 5 years of the study period. Long-term complications encountered included neurological, respiratory and cardiac problems. Conclusion: ECMO is a life-saving modality for neonatal and paediatric patients with cardiopulmonary failure from diverse causes. Patients with persistent need for inotropes during ECMO had poorer outcome. Centre experience had an impact on ECMO outcome.

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Key words: Complications, Retrospective, Survival

Introduction

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass technique (CPB) introduced by Bartlett in 1972, which provides life-saving support in patients with refractory yet reversible cardiorespiratory failure until organ recovery or organ transplantation. Since the first report of successful ECMO support in an adult was published by Hill in 1972, there have been over 45,000 cases in the ECMO Registry of Extracorporeal Life Support Organization (ELSO), including over 27,000 newborns and 9000 children.[1]

KK Women's and Children's Hospital (KKH) is an 830-bed tertiary institution for women and children in Singapore with about 26,000 paediatric hospital admissions per year. It is both a local and a regional tertiary referral centre for women and children. It has a 16-bedded multidisciplinary Paediatric Intensive Care Unit (PICU) with about 700 admissions per year and a 32-bedded Neonatal Intensive Care Unit (NICU) with similar yearly admissions. The PICU admits all postoperative cardiac surgical patients weighing more than 2 kg. During the study duration, there was an average of 186.4 cardiac operations per year. ECMO was first

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introduced in KKH in 2002 and our experience has increased significantly over the years. As there was no paediatric heart and lung transplant programme in Singapore, the use of ECMO was only as a bridge to organ recovery.

This retrospective descriptive review aims to report the characteristics of the patients who received ECMO, the primary outcome of survival to hospital discharge and the secondary outcomes of short-term and long-term complications of ECMO.

Materials and Methods

We performed a retrospective chart review on all patients who received ECMO in the PICU and NICU between January 2002 and December 2012. The first patient was a child with viral myocarditis and complete heart block. In 2006, we started ECMO in NICU on neonates with refractory respiratory failure secondary to meconium aspiration syndrome (MAS) and congenital diaphragmatic hernia (CDH). In 2008, we did our first case of extracorporeal cardiopulmonary resuscitation (ECPR) on a child with myocarditis. The medical record of each patient was reviewed to determine demographic history (age on admission and gender), primary diagnoses, indications for ECMO, occurrence of cardiac arrest prior to ECMO initiation, location of ECMO initiation, type of ECMO (veno-venous or veno-arterial) and duration of ECMO support as detailed below, complications while on ECMO (neurological, respiratory, mechanical, cardiac, haemorrhagic), survival to hospital discharge, and long-term complications. Indications for ECMO were categorised into respiratory, cardiac or ECPR. Respiratory and cardiac indications were defined by the primary organ system involvement. We classified the complications during ECMO into haemorrhagic, neurological, mechanical, renal and cardiac complications. Long-term complications were classified into neurological, respiratory, developmental or behavioural and late deaths (defined as death any time after hospital discharge) and other problems.

The indications for placement on veno-arterial ECMO (VA ECMO) included poor systemic perfusion with metabolic acidosis and impaired ventricular function by transthoracic echocardiography (TTE) despite optimising inotropic support and fluid status. Patients were started on ECMO flows of about 20 to 30 ml/kg/min and increased to achieve flows according to the body weight: infants – 120 to 150 ml/kg/min; children – 100 to 120 ml/kg/min; and adolescents – 70 to 80 ml/kg/min. Inotropic support would be weaned while maintaining a central venous oxygenation of >65% and then discontinued after commencement of ECMO as far as possible. When there was absence of aortic valve opening due to poor left ventricular function, a left atrial vent would be inserted if the patient had central cannulation with an open chest. We did not perform atrial septal dilatation.

Veno-venous ECMO (VV ECMO) was indicated when there was severe respiratory failure despite high ventilator pressures and fractional inspired oxygen (FiO_2). ECMO flows were started as per VA ECMO flows.

ECMO was performed using centrifugal pumps RotaFlow (Maquet) or Levitronix with a membrane oxygenator Lilliput (Sorin) or Hilite® (Medos). Arterial cannulae used in our institution are from Medtronic DLP® or Maquet, while venous cannulae are the Medtronic Bio-Medicus®, Medtronic DLP® or Maquet.

Management while on ECMO involved ventilatory settings of PIP <30 cm H_2O, PEEP 6 cm to 12 cm H_2O, ventilator rates 15 to 25 breaths per minute and FiO_2 21% to 40%.

ECMO patients were managed by a multidisciplinary team of intensive care physicians, cardiologists, cardiothoracic surgeons and pulmonologists. Daily patient care was performed by both intensive care nurses and the ECMO circuit management, which was carried out by perfusionists trained in cardiopulmonary bypass and ECMO. Systemic anticoagulation was done with intravenous unfractionated heparin infusion to achieve an activated clotting time (ACT) of between 180 to 220 seconds. When there was severe bleeding, the ACT target would be reduced to 160 to 180 seconds until the bleeding was controlled. Blood products were transfused to maintain a platelet level more than 80 x 10^{12}/L, a haemoglobin level more than 10 g/dL, a prothrombin time less than 17 seconds and a fibrinogen level more than 1 g/L.

ECMO circuits were changed if there were indications of haemolysis evidenced by haemoglobinuria, decreasing haematocrit and rising indirect bilirubin or evidence of clots in the circuit.

Duration of support was determined by readiness to wean, and was in turn based on assessment of the recovery of cardiopulmonary function by clinical assessment, chest X-ray and TTE. ECMO flow rates were weaned over a few hours to a day and the decision to decannulate was based on the stability of the patient on conventional treatment for about 30 minutes off ECMO. For patients with irreversible organ failure, the decision to discontinue ECMO was made by a multidisciplinary team of intensive care physicians, cardiologists and pulmonologists together with the families.

All records were reviewed as hard or digital copies. Descriptive statistics were reported as median, range, and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. Categorical variables were analysed using a Fisher's exact test or Pearson chi-square test, whereas continuous variables

were analysed using a Mann-Whitney U test or the Kruskal-Wallis test when comparing more than 2 groups. All statistical analysis was performed using SPSS 19.0. Significance was determined as $P < 0.05$.

Results

During the 11-year period, there were a total of 48 patients who received ECMO in both the PICU and NICU. Twenty-six were females and 22 were males. The median age at ECMO initiation was 20 months (range, newborn to 23 years). The 23-year-old was admitted to the PICU after surgery for congenital heart disease and had ECMO initiated in PICU postoperatively. Our first case of ECMO was performed in 2002 and numbers increased with a peak in ECMO use in 2008 (Fig. 1). The median duration of ECMO was 6 days (IQR, 4.0 to 8.8).

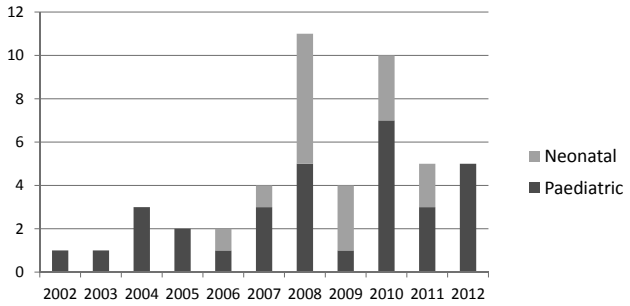

Fig. 1. Number of ECMO cases by year.

Among the neonates, the most common underlying diagnoses were congenital heart disease (CHD) (35.7%), CDH (28.6%) and MAS (28.6%). In the paediatric patients, acute myocarditis (55.9%) and CHD (29.4%) including 2 cases of left pulmonary artery (LPA) sling were the more common diagnoses (Table 1).

Overall, ECMO was initiated mainly for cardiac indications (60.4%). However, respiratory ECMO was more commonly performed in the neonatal population (Table 1). Majority (91.7%) received VA ECMO, both in the paediatric and neonatal group (Table 2).

Thirty-three patients (68.8%) had ECMO initiated in the ICUs, 28 in the PICU and 5 in the NICU. Thirteen patients (27.1%) had central cannulation and ECMO initiation in the operating room. Of the 2 remaining patients, one had ECMO started in our Emergency Department and another in a separate tertiary hospital before being transferred back to our ICU.

Data on complications during ECMO was missing in 1 patient. Of the 47 patients with available data, all except 1 experienced at least 1 complication during ECMO. Haemorrhagic complications, especially around the cannula site and mucosal bleeding, were common (Table 3). One-third of the patients required renal replacement therapy. Neurological complications occurred in 6 patients, 4 of whom were declared brain dead during ECMO. All of these patients had myocarditis and the mortality rate was 80%.

Table 1. Survival Outcomes by Age Group and Indications

	No. of Infants	Survive ECMO		Survive to Discharge	
		n	%	n	%
Neonatal					
Respiratory	-	-	-	-	-
MAS	4	4	100.0	4	100.0
CDH	4	3	75.0	2	50.0
Cardiac (postcardiotomy)	5	2	40.0	1	20.0
ECPR (arrhythmia)	1	1	100.0	1	100.0
Total	14	10	71.4	8	57.1
Paediatric					
Respiratory	-	-	-	-	-
ARDS	2	2	100.0	2	100.0
Interstitial lung disease with pulmonary hypertension	1	0	0.0	0	0.0
LPA sling with tracheostenosis	2	0	0.0	0	0.0
Cardiac	-	-	-	-	-
Myocarditis	19	13	68.4	10	52.6
Postcardiotomy	8	5	62.5	1	12.5
Sepsis	2	25	100.0	2	100.0
Total	34	21	61.8	14	41.2
Grand Total	48	31	64.6	22	45.8

ARDS: Acute respiratory distress syndrome; CDH: Congenital diaphragmatic hernia; ECMO: Extracorporeal membrane oxygenation; ECPR: Extracorporeal cardiopulmonary resuscitation; LPA: Left pulmonary artery; MAS: Meconium aspiration syndrome

Table 2. Indications and Types of ECMO

	Indications	n	Types	n
Neonatal (n = 14)	Cardiac	5	VA	13
	Pulmonary	8	VV	1
	ECPR	1		
Pediatric (n = 34)	Cardiac	24	VA	30
	Pulmonary	6	VV	3
	ECPR	4	VA -> VV	1

ECMO: Extracorporeal membrane oxygenation; ECPR: Extracorporeal cardiopulmonary resuscitation; VA: Veno-arterial ECMO; VV: Veno-venous ECMO; VA -> VV: Veno-arterial ECMO with subsequent conversion to veno-venous ECMO

Table 3. Complications During ECMO

Complications		n (% of Total Cases)
Mechanical	Cannula kinking	2 (4.2)
	Clots	6 (12.5)
Haemorrhagic	GIT	7 (14.6)
	Cannula site	18 (37.5)
	Surgical site	2 (4.2)
	DIC	6 (12.5)
	Mucosal	14 (29.2)
	Lung	5 (10.4)
	Haemothorax	3 (6.3)
Neurologic	Brain Death	4 (8.3)
	Cerebral infarction	1 (2.1)
	Intracranial bleed	2 (4.2)
	Seizures	1 (2.1)
Renal	Needing renal replacement therapy	15 (31.3)
Cardiovascular	Inotropes	11 (22.9)
	Vasodilators	11 (22.9)
	CPR	2 (4.2)
	Pericardial effusions	2 (4.2)
Others	Pneumothorax	4 (8.9)
	Pericardial clot	3 (6.3)
	Wound site infection	1 (2.2)

ECMO: Extracorporeal membrane oxygenation; CPR: Corporeal cardiopulmonary resuscitation; CPR: Cardiopulmonary resuscitation; DIC: Disseminated intravascular coagulation; GIT: Gastrointestinal tract

Thirty one (64.6%) patients survived ECMO decannulation but eventually 22 patients (45.8%) survived to hospital discharge. Survival was highest in the group of neonates who required ECMO for respiratory indications at 75%, with 100% survival in patients with MAS and 50% in those with CDH (Table 1). The survival rates in postcardiotomy patients who required ECMO were low for both the neonatal and paediatric groups (20% and 12.5%).

Of the 22 survivors, 6 (28.6%) had long-term neurological deficits which included foot drop, sensorineural deafness, left hemiplegia, epilepsy and oropharyngeal dysphagia. Developmental problems such as poor attention and speech delay were seen in 2 patients (9.5%) and 4 others (19.0%) developed reactive airway disease after discharge. Late death occurred in 2 of our patients (9.1%) who survived hospital discharge. One patient had complex CHD who died after 5 months despite repeated surgeries, and the other had myocarditis that progressed to end-stage cardiomyopathy and died 17 months later due to decompensated cardiac failure.

We performed univariate analysis comparing age group (paediatric or neonatal), gender, pre-ECMO cardiac arrest, duration of ECMO, occurrence of cardiac arrest before ECMO (ECPR included), time period (2002 to 2007, 2008 to 2012), need for renal replacement therapy, need for inotropic support, hypertension requiring vasodilators and acute neurological complication while on ECMO with survival to hospital discharge (Table 4). Need for inotropic support during ECMO was associated with lower survival. Patients with hypertension had better survival.

Discussion

This is the largest series of paediatric and neonatal patients who received ECMO support in a single centre over an 11-year period in Singapore. In the early years of our experience, ECMO was considered primarily for patients who were in cardiac failure refractory to maximum medical therapy.

Our survival rates in MAS and CDH patients did not differ from international experience of 94% and 50% respectively.[1] In a Cochrane meta-analysis of neonatal ECMO for respiratory failure, ECMO was shown to have a clear benefit on survival.[2] The relative risk of death before discharge was 0.44 with ECMO compared to conventional treatment. This effect was more pronounced when CDH was excluded from the analysis. The utility and benefit for ECMO in CDH was therefore less clear. While the acute lung injury and associated pulmonary hypertension in MAS is often reversible, underlying pulmonary hypoplasia

Table 4. Age Group, Pre-ECMO Arrest, Time Period, Renal Replacement Therapy and Inotropic Support on ECMO — Survivors Compared with Non-Survivors

	Survivors (n = 22, %)*	Non-Survivors (n = 26, %)*	Significance (*P* Value)
Age group			
Paediatric	14 (63.6)	20 (76.9)	0.31
Neonatal	8 (36.4)	6 (23.1)	
Gender			0.38
Female	10 (45.5)	16 (61.5)	
Male	12 ((54.5)	10 (38.5)	
Duration of ECMO	7.0 (5.0, 9.0)	5.0 (2.8, 8.2)	0.17
Pre-ECMO arrest	7 (31.8)	14 (53.4)	0.19
Period			
2002-2007	3 (13.6)	10 (38.5)	0.1
2008-2012	19 (86.4)	16 (61.5)	
Renal replacement therapy	5 (22.7)	10 38.5)	0.24
Inotropic support on ECMO	1 (4.5)	10 (38.5)	0.006
Hypertension requiring vasodilators	10 (45.5)	1 (3.8)	0.001
Neurological complications	2 (9.1)	5 (19.2)	0.43

ECMO: Extracorporeal membrane oxygenation
*Data are represented as median (IQR)

and persistence of pulmonary hypertension affect the reversibility of pulmonary failure in CDH. Risk factors identified to be associated with in-hospital mortality in patients with CDH on ECMO were prenatal diagnosis of CDH, low 5-minute Apgar score of ≤6, low birth weight (<2 kg), $PaCO_2$ higher than 60 mm Hg during the 6-hour period before ECMO, total ECMO duration of 15 days or longer, and the complications of intracranial haemorrhage, PDA right-to-left shunt, requirement of CPR, haemolysis with plasma haemoglobin of more than 0.5 g/L, surgical site haemorrhage, disseminated intravascular coagulation (DIC), and requirement of dialysis while on ECMO.[3]

Survival rates in postcardiotomy patients improved from 0% in the earlier period (2002 to 2007) to 25% in the later period and this could be accounted for by the higher threshold for starting ECMO in the earlier period with patients at a physiologically poorer pre-ECMO state. ECMO was considered when the patients had failed maximal medical treatment with high inotropic and ventilatory support. Many of them likely had profound circulatory failure before ECMO was commenced. Pre-ECMO severe metabolic acidosis, in addition to underlying cardiac diagnoses and complexity of the cardiac surgery, had been found to influence survival for postcardiotomy patients supported on ECMO.[4,5] The absence of a heart and lung transplant programme in our centre also precluded the option of organ replacement as an exit strategy for ECMO.

All but 1 had at least 1 complication while on ECMO. Our incidence of mechanical, haemorrhagic and cardiovascular complications were generally lower than reported in the ELSO Registry, while neurological and renal complications were similar to international rates.

Known significant pre-ECMO predictors of mortality include severe metabolic acidosis[4,6] single ventricle physiology and history of stage-1 procedure for cardiac disease.[4] During ECMO, complications such as neurological injury,[4,7,8] renal dysfunction,[5,6,7] persistent metabolic acidosis,[4,6] arrhythmias[8] and bleeding[8] as well as prolonged duration of extracorporeal life support (ECLS),[5,7,9] repeat need for ECLS,[7] absence of heart transplantation[7] and need for inotropes[6,10] had been found to be significant factors for hospital mortality. In a series of paediatric ECPR cases, acute neurological injury defined as brain death, intracranial bleed and cerebral infarction was not uncommon (22%), with a high mortality rate of 89%.[11] Those with cardiac disease, less metabolic acidosis pre-ECMO and uncomplicated ECMO course had reduced odds of neurological injury.

We analysed various factors including age groups, gender, pre-ECMO cardiac arrest, duration of ECMO, need for inotropic support during ECMO, hypertension, acute neurological injury, need for renal replacement therapy and duration of ECMO with survival to discharge. Similar to other studies,[6,10] the need for inotropic support during ECMO was a poor prognostic indicator and the converse was true for hypertension requiring vasodilator use. The need for renal replacement therapy, however, was not associated with a survival difference.

Systemic hypertension is a recognised complication of ECMO, especially in the neonatal patients. It occurred in 38.4% to 88% of neonatal ECMO patients in reported

series.[12,13,14] The mechanism of hypertension in ECMO patients is not entirely clear. It is believed that the augmented stroke volume in VA ECMO from the return flow into the aorta contributes to the increase in blood pressure.[12,13] Alteration in water and sodium handling has also been postulated to be a potential cause.[13] Intracranial haemorrhage (ICH) was shown to be more common in neonates on ECMO with hypertension.[13] Similar finding was not found in a paediatric series of VV ECMO.[15] Significant hypertension was also not significantly associated with survival.[14,15] In our study, 1 of the 2 patients with ICH had hypertension requiring vasodilator therapy. However, the temporal relationship of the onset of hypertension and ICH was not clear as this patient had radiological confirmation of ICH only after ECMO was discontinued. Intracranial hypertension as the cause of systemic hypertension, therefore, could not be excluded. Interestingly, hypertensive patients in our cohort had better survival. This was true even after excluding patients who required inotropic support. We treated hypertension readily with afterload reduction agents which could have augmented cardiac output from the external ECMO flow and the native heart.

Although not statistically significant in our small sample, the survival more than doubled in the later period compared to the first 6 years of our experience, from 23% to 54%. The improvement through experience of the ICU team and better coordination of multidisciplinary teams were the likely contributory factors.

Occurrence of cardiac arrest before ECMO in 21 patients, which included 4 ECPR cases, was not found to affect survival. The state of the patient pre-ECMO had a greater impact on survival, which is largely reflected by the presence of severe metabolic acidosis.[4,7,16] We did not, however, study pre-ECMO acidosis in this study. A recent report from the National Registry of Cardiopulmonary Resuscitation in the United States on ECPR in the neonatal and paediatric population cited a survival of 43% with good neurological outcome in survivors.[16]

Long-term outcomes in the neonatal ECMO patients have been studied,[17] but there is a paucity of similar studies in the older paediatric population, especially in children who had non-cardiac indications for ECMO. We studied the long-term complications such as late death, re-admissions, as well as neurological, respiratory, developmental and other complications.

About one-third of our survivors suffered long-term neurological sequelae. The most severe case of neurological injury was seen in an 8-year-old child with fulminant myocarditis who developed intracranial bleed while on ECMO and the complications of epilepsy, left hemiplegia, right vocal cord paresis and oropharyngeal dysphagia. Debilitating neurological injury was also not uncommon in other paediatric ECMO series.[18]

The UK Collaborative ECMO trial is the largest randomised controlled trial in neonatal ECMO to date, with follow-up data up to 7 years.[19,20] The trial showed a clear benefit of ECMO on survival compared to conventional treatment and this benefit was not offset by increased morbidities at the 7-year follow-up in terms of neurocognitive or behavioural impairment. Long-term effects on neurocognition and behaviour were observed in both ECMO and conventional arms, with 24% exhibiting cognitive delay. This suggested that in these sick neonates, the underlying disease and physiological compromise had a major influence on long-term neurological outcome.

Limitations

This is a case series of a single centre — the results may be specific to the local patient population, surgical expertise and techniques, support strategies and infrastructure. Further limitations include the retrospective nature of this study.

Conclusion

ECMO is a life-saving modality of treatment for patients with refractory cardiopulmonary failure of a diverse aetiology, especially in the neonatal patients with respiratory failure. The overall survival rate in our series was 48.5%. Short-term and long-term complications were not uncommon in ECMO patients. Centre experience appeared to have an impact on patient survival on ECMO, highlighting the need for continuing quality assurance and improvement for the ECMO programme.

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