Outcome of Extracorporeal Membrane Oxygenation for Neonatal Refractory Respiratory Failure

Dear Editor,

Introduction

Extracorporeal membrane oxygenation (ECMO), a well-established intervention for refractory respiratory failure in neonates was introduced to Singapore in January 2008. This series reviews the outcome of neonates who underwent ECMO from January 2008 for over a 4-year period.

Materials and Methods

Data were collected from a prospectively maintained database and retrospective chart review. The data collected included maternal and neonatal characteristics, aetiology of respiratory failure, oxygenation index (OI) and alveolar-arterial oxygen gradient ($AaDO_2$) prior to undergoing ECMO, age of commencing ECMO, duration of ECMO, complications, duration of hospitalisation and follow-up. Nitric oxide was commenced when the OI was ≥15 as per unit protocol.

Results

Nine neonates met the ECMO criteria, out of which 7 neonates (congenital diaphragmatic hernia (CDH): n = 4 and meconium aspiration syndrome (MAS): n = 3 and death before procedure (MAS): n = 2) underwent ECMO during the study period. One neonate died of hypoxia secondary to respiratory failure while awaiting blood products for ECMO. Second neonate died during cannulation attempt from hypoxia and bleeding from internal carotid artery tear. All neonates with CDH were diagnosed during the antenatal period. Their median birth weight was 2.94 kg (range, 2.58 to 3.29 kg) and gestational age was 38 weeks (range, 37 to 39 weeks) respectively. The median OI and $AaDO_2$ prior to initiating ECMO in CDH neonates was 58.8 (range, 19.2 to 72.25) and 619.5 mmHg (range, 496 to 641.5 mmHg) respectively. It was 37.16 (range, 26.5 to 41) and 619 mmHg (range, 612 to 621 mmHg) respectively for non-CDH neonates. Median age at starting ECMO was 2 days (range, 1 to 15 days). All neonates required high frequency oscillatory ventilation (HFOV), inhaled nitric oxide and triple ionotropes. Neonate number 2 was cannulated for ECMO following CDH repair. The ECMO variables are shown in Table 1.

The ECMO circuits comprised a centrifugal pump (Rota flow) and a membrane oxygenator (Lilliput II, Sorin Group, Italy). Phosphorylcholine-coated circuits were used in all the cases. All neonates underwent cannulations of the neck vessels using the open technique. Six neonates had cannulation of the right common carotid artery and internal jugular vein using Fr 8 and 10 MAQUET (MAQUET INC, Bridgewater, USA) catheters for veno arterial (VA) ECMO. Neonate number 5 underwent veno venous (VV) ECMO. Neonate number 7 was on VA ECMO for the first 4 days. First attempt to wean the baby off ECMO failed on day 4. As the echocardiogram demonstrated good cardiac function and maximum flow attained with VA cannula was suboptimal, the neonate was converted to VV ECMO with Fr 12 MAQUET VV catheter at the time of failed weaning attempt. The median duration of ECMO for all cases was 6 days (range, 3 to 16 days). Median duration of ECMO for CDH and non-CDH neonates were 9 days (range, 4 to 16 days) and 4 days (range, 3 to 6.8 days) respectively.

Haemofiltration was required in 3 neonates (42.9%), thrombocytopenia developed in 5 neonates (71.4%),

Table 1. ECMO Characteristics in 7 Neonates Who Underwent ECMO

Patient No.	Age of Initiation (days)	Type of ECMO	Duration (days)	Hospitalisation days	Survival	Feeding at discharge
1	2	VA	16	83	Yes	Bottle feeding
2	15	VA	6	70	No	NA
3	4	VA	4	34	Yes	Bottle feeding
4	2	VA	4	39	Yes	Bottle feeding
5	1	VV	10	10	No	NA
6	1	VA	3	32	Yes	Bottle and NG feeding
7	3.5	VA+VV	6.8	41	Yes	NG feeding

ECMO: Extracorporeal membrane oxygenation VA: Veno arterial ECMO; VV: Veno venous ECMO; NG: Nasogastric; PEG: Percutaneous endoscopic gastrostomy

thrombosis requiring circuit change was present in 1 neonate (14.3%), significant haemorrhage in 1 neonate (14.3%) and hypertension requiring treatment in 2 neonates (28.6%). Overall, 5 neonates survived ECMO (71.4%). Two neonates developed intracranial haemorrhage (ICH) (28.6%). Left frontal periventricular white matter cyst and intraparenchymal haematoma of right cerebellar hemisphere were seen in neonates 2 and 6 respectively. All neonates received platelet transfusions for thrombocytopenia.

Neonates with bleeding responded to the use of fresh frozen plasma blood and platelets to optimise coagulation status and haematological values. Bleeding from the neck cannulation site was controlled by tightening snares and use of pressure dressing. Neonate with hypertension was managed with continuous infusion of hydralazine, glycerin trinitrate and sodium nitroprusside.

Survival in CDH neonates was 50% (2/4). All 3 neonates (100%) with MAS survived. Median duration of hospital stay was 39 days (range, 10 to 83 days). Four out of 5 surviving neonates were thriving well on formula feeds at the time of discharge. Neurodevelopmental follow-up was performed at regular intervals, and 4 out of 5 (80%) neonates had intact neurodevelopmental outcome at 12 to 36 months of age. Neonate number 7 had severe bilateral sensory neural hearing loss requiring hearing aids with expressive speech and language delay.

Indications for ECMO

Inclusion Criteria	
Respiratory Entry Criteria	
(i) $AaDO_2$	>605 to 620 mmHg for 4 to 12 hours
(ii) Oxygenation Index (01)	>35 to 60 for 0.5 to 6 hours
(iii) PaO_2	<35 to <60 mmHg for 2 to 12 hours
(iv) Acidosis and shock	pH < 7.25 for 2 hours or with hypotension
(v) Acute deterioration	PaO_2 < 30 to 40 mmHg
• Gestational Age ≥34 weeks	
• Birthweight of ≥2.5 kg	
• Reversible lung disease with length of mechanical ventilation ≤14 days	
• The absence of uncontrolled bleeding or coagulopathy	
• No intracranial haemorrhage ≥grade III	
• No uncorrectable congenital heart disease	
• Failure of optimal medical management	
• Decision to provide full management support	
Exclusion Criteria	
Lethal anomalies such as Trisomy 13, 18 and documented severe irreversible brain injury	

$$AaDO_2 = (713 \times F_iO_2) - \frac{(PaCO_2 + PaO_2)}{0.8}$$

$$OI = \frac{MAP \times F_iO_2 \times 100}{PaO_2}$$

Discussion

This study describes our experience during the formalisation phase of ECMO programme. This is the first study that looked at the outcome of neonates who underwent ECMO in the country. Majority of infants in our series had CDH. Indications for ECMO in CDH infants are not consistent in literature as compared to non-CDH infants (Table 2). However there is agreement on the need for less stringent ECMO criteria in CDH to reduce lung injury prior to placing the neonates on ECMO.[1] We followed the lower end of the respiratory entry criteria as the indication for ECMO in CDH, which may be reviewed in future.

In the absence of randomised control trials (RCTs) to compare the efficacy of VV versus VA ECMO, available evidence support the use of VV ECMO in neonates without significant myocardial depression. Those with mild to moderate ionotropic support recover once on ECMO.[2] Complications with cannula and haemolysis are likely to be higher with VV ECMO whereas bleeding is higher with VA ECMO. Our current policy, however, is to offer VA ECMO for all neonates with CDH and congenital heart disease (CHD). We offer VV ECMO to non-CDH neonates if cardiac compromise is not significant .

Complications are common in neonatal ECMO. Significant bleeding, haemolysis requiring circuit change, need for haemofiltration, ICH, hypertension and clot formation in the circuit requiring change of circuit were the major complications in our series.

We defined bleeding as significant when thoracotomy or haemothorax drainage of more than 4 mL/kg/hour or gastrointestinal (GI), oral, nasal, catheter, and cannula site bleeding with decreasing haematocrit despite intervention. The basic principles underlying the management of bleeding are optimisation of coagulation, drug therapy and surgical treatment. We decreased heparin infusion rate to 50%, accept activated clotting time (ACT) of 150 to 180 seconds, keep haemoglobin (Hb) level more than 12 g/dL, platelets more than 120,000, prothrombin time of less than (PT) 15 seconds and fibrinogen level of more than 1.5g/L. Epsilon amino caproic acid (EACA) is the most widely used antifibrinolytic drug, when medications are required to control bleeding. We use tranexamic acid in view of the non-availability of EACA. Large amount of blood clots in a body cavity act as a potent stimulus for fibrinolysis and this causes a vicious cycle of ongoing bleeding. Timely and often repeated surgical exploration is the only way out of this situation. We considered haemolysis significant when there is (i) increase in plasma-free haemoglobin, (ii) reddish discoloration of the urine and (iii) continuing drop in the haematocrit level without obvious signs of bleeding. Management steps include identification and correction of causes. Main causes are difficulties with cannula position

producing turbulence, clot formation in the circuit and high negative suction pressure in the venous cannula (≥30mmHg). Centrifugal pumps cause higher haemolysis. When there is haemolysis associated with high plasma-free Hb alone, one should consider changing pump head. However in case of consumptive coagulopathy, changing pump head and circuit may need to be considered. Haemofiltration reduces fluid overload and use of furosemide, thereby reducing nephrotoxicity, ototoxicity and removes inflammatory mediators. No RCTs are available to date to determine the efficacy of haemofiltration on ECMO. In a recent case comparison study involving 61 neonates on ECMO, haemofiltration showed a reduction in the number of days on ECMO and mechanical ventilation. It was postulated that addition of haemofiltration to ECMO circuit reduces systemic inflammatory response syndrome (SIRS) and capillary leakage syndrome. It has also been shown to reduce number of blood transfusions and cost per ECMO run.[3] Hypertension is seen more frequently in neonates on VA ECMO than VV ECMO. Systemic hypertension is seen in 15% of ECMO patients according to the July 2005 ELSO report.[4] It should be treated aggressively. The risk of bleeding including IVH is significantly higher in neonates with hypertension.[5] We recommend treatment of hypertension when it is persistently above the 50th to 90th percentile range. In a term neonate, this would amount to systolic BP of 80 to 90 mmHg, diastolic BP of 50 to 65 mmHg and mean BP of 60 to 75 mmHg.[6] Hypertension maybe resistant to treatment while on ECMO.

Clot formation within the circuit is unavoidable; it can be limited by maintaining adequate heparinisation and circuit flow rates. Oxygenator is the commonest site of clot formation followed by the bridge and tubings, especially on venous side and connection sites. Two concerns about clots in circuit are (i) circuit may clot, leading to obstruction of blood flow in the circuit and (ii) the potential for clots to embolise to the patient. Circuit is changed if clots are seen on the arterial side of the circuit. Circuit change is also undertaken if clots on venous side produce obstruction to blood flow or infant develop disseminated intravascular coagulation (DIC) characterised by visible clots, rising D dimer values, fibrinogenemia and platelet consumption.

Our post ECMO survival was comparable to published literature. Two neonates died in our series. Neonate number 2 was successfully decannulated from ECMO on day 6 of ECMO but died of multi-organ dysfunction secondary to sepsis on day 71 of life. Neonate number 5 with primary diagnosis of CDH was initiated on VV ECMO. The infant developed cardiac arrest on day 10 of ECMO before CDH could be repaired. Parents refused postmortem examination. We were preparing the neonate for haemodialysis at the time of cardiac arrest. We concluded that the cardiac arrest was related to renal failure.

One neonate was found to be developmentally delayed during follow-up and our results were comparable to published literature.

We faced delay in obtaining blood products and cannulation issues in the initial phase of the programme. Both issues have been resolved by establishing specific protocols, multidisciplinary teams comprising respective specialists, ECMO simulation and education of the team members. We are in the process of formalising an ECMO specialist training programme.

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