Extracorporeal Membrane Oxygenation in Premature Infants With Congenital Diaphragmatic Hernia

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Prematurity and low birth weight have been exclusion criteria for extracorporeal membrane oxygenation (ECMO); however, these criteria are not evidence based. With advances in anticoagulation, improved technology, and surgical expertise, it is difficult to deny a potential therapy based on these criteria alone. We report the outcome of three neonates who were ineligible based on traditional criteria but were offered ECMO as a life-saving measure. We highlight the interdisciplinary nature of modern decision-making. All three neonates had severe congenital diaphragmatic hernia diagnosed prenatally, had normal fetal karyotypes, were born prematurely, and weighed less than 2 kg. All three neonates underwent cervical venoarterial cannulation, stabilization on ECMO, and repair of their congenital diaphragmatic hernia early in their ECMO courses. All three infants had long courses of respiratory support attributable to lung hypoplasia, but there were no short- or long-term complications attributable to ECMO support directly. All three are alive at 2 years of age and were making progress developmentally. In conclusion, with interdisciplinary collaboration and clinical guidelines uniformly implemented, low birth weight infants may benefit from ECMO and should not be denied the therapy arbitrarily based on gestational age or size alone. Further research is essential to determine appropriate patient selection in premature infants. ASAIO Journal 2018; 64:e126–e129.

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Case Series

The first report of newborns supported with extracorporeal membrane oxygenation (ECMO) was in preterm neonates.1 However, these infants were reported to suffer a high incidence of intracranial hemorrhage (ICH), resulting in high mortality.2 Thus, gestational age (GA) less than 34 weeks was said to be a general contraindication for support with ECMO.3 We acknowledge that a review of the literature suggests that institutional approaches to ECMO beyond the limits of typical exclusion criteria are variable. There have been a few reports in which data were mined from the extracorporeal life support organization (ELSO) registry challenging both GA (<34 weeks) and weight criteria (<2 kg). In a study by Hirschl et al.,4 they reported on patients born between 32 and 42 week gestation and found survival rates in patients 34 and 6/7 or lower GA to be 63% and in patients less than 2.0 kg to be 65%. There were no patients under 32 weeks, and the average birth weight of the low birth weight (LBW) infants was 1.8 ± 0.1 kg. Another report by Rozmiarek et al.5 found that LBW infants (<2 kg) had a reasonable survival. In this report, the infants were just below 2 kg (1.9 ± 0.2 kg), and the mean GA was 35.2 weeks. Furthermore, they predicted statistically that infant at 1.6 kg would have a 40% survival rate, though they emphasized that this “does not account for technical considerations regarding the size of the internal jugular vein or common carotid artery.” The most recent report from the ELSO registry demonstrated reasonable survival rates in premature infants, though they compared neonates between 29 and 33 weeks gestation (86% were 32–33 weeks gestation) to neonates born at 34 weeks gestation and the mean birth weights 2.28 and 2.49 kg, respectively.6 Thus, there are little to no data about babies born less than 34 weeks and less than 2 kg, and all three of the reports mining the ELSO database indicated that being LBW or premature with the diagnosis of congenital diaphragmatic hernia (CDH) lead to marked decreases in survival. These ELSO registry analyses that we summarized covered the time period through 2008, and we added a query of the database from 2010 to 2015 and found 174 infants born at 2 kg or less than 34 weeks and found that overall 35% survived until discharge in the group less than 2 kg and 40% less than 34 weeks gestation, though the details lacked data of patients who met both age and weight criteria.

During the time period of 2010 to 2015, our center had 60 neonates supported with ECMO; four were less than 2 kg. The 4th case was not premature (37 [4/7] weeks) and, thus, not presented here. This report is a case series that describes the perinatal course and outcome of infants born prematurely, who were less than 2 kg, and who all had CDH requiring ECMO support. This report challenges the position that there are relative contraindications for ECMO in patients with extremely severe anatomic and physiologic derangements.

Case 1

The patient was prenatally diagnosed with a left CDH and on imaging had a lung head ratio (LHR) of 1.1 at 28 weeks. The fetal karyotype was normal, but it was noted on fetal imaging that the fetus had unilateral cleft lip/palate and left hydronephrosis. The patient was born at 31 4/7 weeks gestation after...
the mother had a placental abruption and the patient was delivered via precipitous vaginal delivery with no exposure to antenatal steroids. The patient was intubated and given surfactant in the delivery room with Apgar scores of 1, 1, and 3 at 1, 5, and 10 minutes, respectively. The first measured weight was 1,800 grams. On admission, the head ultrasound showed evidence of bilateral choroid plexus cysts, and a left germinial matrix hemorrhage could not be excluded. A postnatal echocardiogram showed depressed biventricular function with evidence of supra-systemic RV pressures and a large patent ductus arteriosus with a bidirectional ductal shunt.

By 12 hours of life, the patient’s condition deteriorated despite maximum intensive care short of ECMO. There were concerns for a genetic diagnosis given the physical findings of hypertelorism, small and down slanting palpebral fissures, cleft lip and palate, and a short neck with mild nuchal thickening. After an interdisciplinary discussion which included the family, we chose to proceed to support with ECMO despite not meeting traditional ECMO inclusion criteria.

Venoarterial (VA) ECMO was initiated at 20 hours of life with 8 Fr arterial and 8 Fr venous cannulas. On day of life (DOL) 2, a cranial ultrasound revealed a grade II intraventricular hemorrhage (IVH) that remained unchanged through discharge. The diaphragmatic hernia was repaired while on ECMO support on DOL 3. The patient weaned off ECMO on DOL 6. She met clinical criteria for the diagnosis of Fryns Syndrome. The patient had a prolonged course of mechanical ventilation and could not tolerate nasal continuous positive airway pressure caused by the cleft lip and palate and had a tracheostomy performed. She was discharged home with a tracheostomy and respiratory support on conventional mechanical ventilation for respiratory support. She is now 4 years old and had her tracheostomy removed when she was 3 years old. She was diagnosed with posthemorrhagic hydrocephalus, though decompression was not required. The patient was seen in the developmental follow-up clinic at Texas Children’s Hospital, which routinely uses the Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) to assess development. At 22 months of life, the CLAMS was at 19 months and CAT was at 21 months.

Case 2

The patient was prenatally diagnosed with a left CDH at 23 weeks gestation and had an LHR of 0.76 on fetal imaging. At 28 weeks gestation, the LHR was 0.88, and her fetal karyotype was normal. The patient met criteria for fetal endoscopic balloon tracheal occlusion (FETO). At 29 weeks, FETO was attempted but unsuccessful as the fetal tracheal could not be accessed in utero. The mother presented with preterm labor and premature rupture of membranes at 31 5/7 weeks, and urgent ex utero intrapartum treatment procedure with ECMO cannulation was planned. At induction of anesthesia but before the ex utero intrapartum treatment procedure could be done, placental abruption was recognized, and the patient was delivered by emergent cesarean section. The patient developed progressive cardiorespiratory deterioration in the operating room despite aggressive resuscitation, and VA ECMO was initiated before transfer to the neonatal intensive care unit (NICU). The arterial and venous catheters were both 8 Fr. Apgar scores were 1, 4, and 7 at 1, 5, and 10 minutes, respectively; the patient’s clinical condition was such that the resuscitation went to cannulation before the patient could be weighed. The weight on admission to the ICU was estimated at 1,500 g.

The patient’s CDH was repaired 24 hours after cannulation. ECMO was discontinued on DOL 5. There was no IVH. The patient was supported with prolonged mechanical ventilation in the NICU, and a tracheostomy was placed at 6 months of life for chronic respiratory support. The patient is now 4 years old and has been off ventilatory support for 6 months. The CAT/CLAMS assessment at 19 months of age showed that CLAMS was at 18 months and CAT was at 14 months.

Case 3

The patient was diagnosed by fetal imaging with asymmetric intrauterine growth retardation and having a left CDH with an LHR of 0.7 at 22 weeks gestation. FETO was not considered because the measurement was artificially low because of a disproportionately large head. The LHR was 1.2 at 32 weeks gestation, and a karyotype was normal. Spontaneous premature labor occurred at 36 3/7 weeks gestation, and the patient delivered with a weight of 1,640 g. Apgar scores were 6 and 9 at 1 and 5 minutes, respectively. At approximately 35 hours of age, VA ECMO was initiated after 8 Fr arterial and venous canulas were placed. The patient’s CDH was repaired on DOL 3, and ECMO was discontinued on DOL 7. There was no ICH noted on any of the cranial ultrasound studies. The patient had clinical findings that were suspicious for the diagnosis of Russell Silver syndrome, which was confirmed on postnatal methylation studies. The patient is now 32 months of age on and off oxygen. The patient also receives her enteral nutrition via a gastrostomy tube. The CAT/CLAMS assessments at 13 months showed CLAMS and CAT at 11 months.

Discussion

ECMO has been observed to improve outcomes in neonates with respiratory failure meeting criteria that indicate high mortality rates if not supported with ECMO. Unfortunately, this life-saving form of support has not been available to small immature babies that meet the arbitrary exclusion criteria based on small size or immaturity even when they meet classic clinical severity criteria for placement on ECMO. The evidence that the historical exclusion criteria are relevant in the present era of neonatal care is lacking, and although the size and GA criteria are not unreasonable, it is possible that it deprives some critically ill neonates of life-saving supportive care. This case series does not test a hypothesis but is a case report of three patients, two of which had a combination of three factors (<2 kg, <34 weeks gestation, and the diagnosis of severe CDH) that, based on the present literature, in many institutions would not be offered support with ECMO. The intent of this report is to make the case that in these patients with a combination of problems that led to long hospitalizations, there seem to be reasonable outcomes so that clinical investigators may consider a systematic study of the long-term outcomes in patients meeting one or more exclusion criteria that are supported on ECMO.3

At the Texas Children’s Hospital fetal center, we sought to improve outcomes in patients with CDH by providing uniform care driven by specific clinical care guidelines that were agreed upon after interdisciplinary discussion. The first guideline was
written and initiated in 2005 and was directed to uniform prenatal and perinatal management of CDH. This includes magnetic resonance imaging of the fetus with a special emphasis on assessing lung volumes, along with fetal echocardiography and multiple discussions among the obstetricians, maternal fetal medicine specialists, pediatric surgeons, fetal-pediatric radiologists, and neonatologists with the families during the prenatal period. These evaluations and interdisciplinary discussions include determining whether a fetus meets criteria for FETO and, if so, additional discussions with the family about enrolling in a research protocol involving FETO (IRB approved H-28021). The discussion with the family also includes the possibility of using ECMO in the postnatal period. Thus, families are prepared for the possibility of support with ECMO in their baby when medically indicated. Furthermore, we considered offering support with ECMO to all patients being evaluated with CDH without regard to their birthweight or GA, and the three patients described herein were the only patients who did not meet classic inclusion criteria for support with ECMO.

The second guideline that we developed is focused on postnatal surgical management of patients with CDH that are supported with ECMO. The guideline's focus is on repair on ECMO within 72 hours of cannulation. The rationale for this guideline is to eliminate the variable of an unrepaird CDH on ECMO, thereby, simplifying the post-ECMO course by eliminating post-ECMO CDH repair.9

Overall Interdisciplinary CDH/ECMO Care

In addition, and similar to the interdisciplinary team involved in the fetal period for the diagnosis of CDH, we also have an ECMO team consisting of ECMO specialists, which are a subgroup of neonatologists and a subgroup of pediatric surgeons within the academic practice who participate in the complex decision-making in patients supported on ECMO. This team is also the clinical decision maker involved in the pre- and postnatal care of patients with CDH, independent of the need for support with ECMO. The ECMO team also includes a subgroup of nurses trained in the nursing care specific for neonatal ECMO and a subgroup of transfusion medicine specialists addressing the management of coagulation/anticoagulation unique to neonatal ECMO. These caretakers round together daily on all patients supported on ECMO and are available for on-call consultations around the clock. We also developed a comprehensive protocol for cardiorespiratory management of all patients with CDH, inclusive of support on ECMO that includes transitioning to the desired flow on ECMO, with an open lung strategy. The current ECMO guidelines at Texas Children’s hospital (TCH) also include aggressive management of fluids in the presurgical period in which we use ultrafiltration initiated in the 6–12 hours after cannulation in patients on ECMO to maintain a net neutral to slightly negative fluid balance. Aggressive ultrafiltration early in the course of ECMO in patients with CDH minimizes edema formation so that the repair is in the setting of a nonedematous patient and on aggressive early parenteral nutrition. Furthermore, in 2012, we transitioned from the use of the Sarns S3 roller pumps to the Rotaflo centrifugal pump.10 In the patients reported herein, the guidelines for managing the flow and blood pressure were the same as we use for all patients meeting inclusion criteria. Immediately after cannulation, the circuit flow is gradually increased more than 15–30 minutes to a test flow rate of 100–125 ml/kg/min. This flow usually provides adequate O2 delivery on VA ECMO as assessed by venous saturations and serial blood lactate concentrations. Subsequent flow adjustments are made per individual patient needs. Adequate ECMO flow is indicated by SaO2 > 90% (prechulatory); SvO2 between 65% and 75%, and arterial lactate concentrations <3.0 and prompt capillary refill. All of the patients reported were on VA ECMO, and so our guidelines for venovenous (VV) ECMO are not included. This team has no specific guidelines for management of blood pressure in that whether a patient had a combination of adequate venous saturations, low lactate concentrations, and good urine output, the blood pressure was viewed, in that context, as being adequate.

Our interdisciplinary approach to anticoagulation included daily interdisciplinary rounds with an expert in transfusion medicine in which a daily plan for coagulation was determined and a member of the transfusion medicine team was available for consultation around the clock. We did not change our approach based on GA, and we adopted the approach of Nankervis et al.,11 in which we used factor Xa inhibition assay to determine how to manage the heparin administration, and we corrected abnormal activated clotting times, both high and low times, with clotting factor administrations (either fresh frozen plasma or cryoprecipitate). This is based on the data that suggest that activated clotting time (ACTs) were independent of heparin infusion so that underlying coagulation should be managed with therapeutic heparin administration to keep the factor Xa inhibition assay in range and replacement of consumed coagulation and anticoagulation factors. Furthermore, we changed our coagulation strategy before operating on ECMO by targeting lower ACTs and treatment with aminocaproic acid to inhibit fibrinolysis.

In addition to the concern about increased mortality in this population, there is also the concern about an unacceptably high rate of ICH. In the ELSO registry, publications previously cited for overall survival in infants less than 34 weeks gestation or less than 2.0 kg. There was a higher rate of ICH in the infants meeting traditional exclusion criteria in all studies than in term babies ranging from 37% in the study reported by Hirschl et al.4 (registry from 1988 to 1991) to 5.5% in the study reported by Rozmiarek et al.5 (registry 1991–2002) in patients under 2.0 kg to 21% in the study reported by Church et al.6 (registry 1976–2008). Although these data are concerning, they indicate that ICH risk may be decreasing as coagulation management evolves and that prematurity is probably a bigger risk factor than is LBW. Interestingly, only one of our patients had an ICH, and the interdisciplinary team was uncertain about whether to continue support with ECMO on this patient. The interdisciplinary team decided to continue support with ECMO, and we were fortunate that the ICH did not extend over the rest of the time period, and despite carrying the diagnosis of posthemorrhagic hydrocephalus, the patient’s ventricles have not have to be decompressed surgically, and the neurodevelopment has been close to normal.

The new guidelines and the intensive interdisciplinary care were in place for the three patients reported herein. These processes were critical and led to a strong relationship between the family and the team so that the parents were fully informed about the risks of ECMO, especially in regards to the lack of information about outcomes in patients supported on ECMO that previously would not have been offered based on GA or small size.
In the first case in this series, Fryns syndrome was suspected. Many centers would view this diagnosis as a contraindication for support on ECMO independent of meeting exclusion criteria for size and GA. That view is reasonable as the neurodevelopmental outcomes have not been reviewed systematically because there are few survivors reported. However, isolated reports lead to uncertainty in the uniform grim prognosis based solely on neurodevelopmental outcomes. Despite the concerns about Fryns syndrome, this patient’s developmental progress has been reasonable through the time frame of this report. The second patient was also premature, and the combination of pulmonary hypoplasia and prematurity led to chronic ventilation with mild developmental delays. This patient’s delays are not profound, and she may benefit further by consistent chronic care that has been reported to be associated with improved neurodevelopmental outcomes in patients with severe BPD. The third patient in this series with the diagnosis of severe intrauterine growth retardation and late prematurity was eventually diagnosed with Russell Silver syndrome after the ECMO course. The family was aware that her size may preclude cannula placement. This patient clearly benefited from support with ECMO and long-term medical issues have been mild, and the respiratory course and support have improved steadily.

All the three patients reported in this series met physiologic inclusion criteria for ECMO and had ominous findings on prenatal imaging of lung volumes. Fortunately, despite the concerns and the operations all done on ECMO and despite long post-ECMO hospitalizations, there was only one patient with an ICH, and to date, their developmental process seems reasonable.

Another reason for exclusion by weight being below 2 kg reflects the difficulty in cannulating small cervical vessels with catheters big enough to provide reasonable ECMO flow/support. In our interdisciplinary discussions, we weighed the consequences of not offering ECMO against the risks of an unsuccessful cannulation attempt. Advances in cannula development with small-sized cannulas being reinforced all the way to the tip has allowed the preservation of adequate flow characteristics even with smaller cannulas. In the three patients in our series, 8 Fr cannulas were sufficient to provide adequate ECMO flow to support these small (<2,000 g) neonates. With careful attention to vessel handling and using an open, cut-down technique, the right internal jugular and common carotid vessels could be cannulated.

Although these patients had relatively uncomplicated ECMO courses and transitioned off ECMO support fairly easily, they all had long and complicated pulmonary courses post-ECMO. It is unclear whether their post-ECMO hospital course was dominated by their pulmonary hypoplasia independently of their size and immaturity or whether the course was dominated by abnormalities or injuries from ECMO itself.

Conclusion

This case series described interventions in patients with CDH that were followed from the fetal period to long-term follow-up as outpatients. The patients were managed with detailed uniform care guidelines for all aspects of care. The combination of collaborative decision-making and adherence to guidelines may improve outcomes in patients previously excluded from support with ECMO and other intense supportive modalities. When critical aspects of ongoing supportive care are established, good comparative effectiveness research should be done to determine whether neonates with severe cardiopulmonary disease may benefit from support with ECMO despite meeting previous, arbitrary exclusion criteria after which, prospective decision-making about the implementation of ECMO can be done based on emerging evidence.

References