ARTICLE IN PRESS
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Journal of the Formosan Medical Association (2016) xx, 1–7

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Extracorporeal membrane oxygenation for neonatal congenital diaphragmatic hernia: The initial single-center experience in Taiwan

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Received 23 February 2016; received in revised form 19 June 2016; accepted 28 June 2016

KEYWORDS
congenital diaphragmatic hernia;
extracorporeal membrane oxygenation;
neonate

Background/Purpose: Extracorporeal membrane oxygenation (ECMO) is a treatment option for stabilizing neonates with congenital diaphragmatic hernia (CDH) in a critical condition when standard therapy fails. However, the use of this approach in Taiwan has not been previously reported.
Methods: The charts of all neonates with CDH treated in our institute during the period 2007–2014 were reviewed. After 2010, patients who could not be stabilized with conventional treatment were candidates for ECMO. We compared the demographic data of patients with and without ECMO support. The clinical course and complications of ECMO were also reviewed.
Results: We identified 39 neonates with CDH with a median birth weight of 2696 g (range, 1526–3280 g). Seven (18%) of these patients required ECMO support. The APGAR score at 5 minutes differed significantly between the ECMO and non-ECMO groups. The survival rate was 84.6% (33/39) for all CDH patients and 57.1% (4/7) for the ECMO group. The total ECMO bypass times in the survivors was in the range of 5–36 days, whereas all nonsurvivors received ECMO for at

Conflict of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2016.06.012

Please cite this article in press as: Hung W-T, et al., Extracorporeal membrane oxygenation for neonatal congenital diaphragmatic hernia: The initial single-center experience in Taiwan, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.06.012

least 36 days (mean duration, 68 days). Surgical bleeding occurred in four of seven patients in the ECMO group.
Conclusion: The introduction of ECMO rescued some CDH patients who could not have survived by conventional management. Prolonged (i.e., > 36 days) ECMO support had no benefit for survival.

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with an incidence of approximately one case in every 2000—5000 live births.[1] The degree of pulmonary hypoplasia and pulmonary hypertension determines the severity of the disease, as well as survival in patients with CDH.[2–4] In addition, early stabilization of the patient is a priority before undertaking surgical intervention for the herniated organ. Hence, management of perinatal pulmonary hypertension is a critical focus in the current treatment of CDH.

In 1975, Bartlett et al[5] reported the first successful use of extracorporeal membrane oxygenation (ECMO) in newborns with cardiopulmonary failure. This technique was soon applied to CDH neonates with severe respiratory distress to provide preoperative stabilization.[6–8] The use of ECMO in CDH neonates, which is widely reported in the USA, has long been debated. A Cochrane review on its use for severe respiratory failure in infants failed to demonstrate a clear survival benefit for neonates with CDH, although many surgeons in the USA and Europe consider ECMO as a treatment option.[9] The experience of using ECMO for neonatal CDH has rarely been reported in Asia[10–12] and has never been reported in Taiwan.

Since 1994, the National Taiwan University Hospital, Taipei, Taiwan has used ECMO as a means of mechanical circulatory support for adults and neonates.[13] In December 1994, the first neonatal ECMO treatment was applied to a newborn that could not be separated from cardiopulmonary bypass after cardiac surgery. However, it was not until 2007 that we successfully used ECMO to treat a neonatal patient with respiratory failure in our hospital. In 2010, we first used ECMO for a patient with CDH. In this paper, we report our experience using ECMO for neonates with CDH and the outcomes of these patients, with and without ECMO support.

Methods

Patients

The 39 CDH neonates who were treated at the National Taiwan University Hospital (Taipei, Taiwan) from 2007 to 2014 were all included in this study. The demographic data, medical treatment, surgical timing, operative findings, and outcome of the patients with CDH were collected via chart review. The ECMO indication, parameters of the ECMO run, and complications of ECMO were prospectively collected for quality assurance.[14]

Management of patients with CDH

After delivery, the neonatal patients were admitted to the neonatal intensive care unit. Infants who presented with respiratory distress were stabilized using standard medical and ventilator therapy. If conventional ventilator therapy failed, high-frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) were applied to patients with severe pulmonary hypertension.

Indications for ECMO

Our indications for ECMO were: (1) an oxygenation index of ≥ 40; (2) an alveolar—arterial oxygen difference > 610 mmHg for 8 hours or an alveolar—arterial oxygen difference > 600 mmHg for 12 hours; or (3) partial pressure of arterial oxygen < 40 mmHg for 2 hours. The decision about consultation for ECMO cannulation was made by the neonatologists caring for the infant.

The ECMO technique

We used veno—arterial ECMO for the first run because of hemodynamic instability. Cannulation was performed by the cut-down method through the internal jugular vein and common carotid artery.[15] The ECMO circuit consisted of a centrifugal pump and a hollow-fiber membrane oxygenator with an integrated heat exchanger (Medtronic, Inc., Anaheim, CA, USA), and all surfaces were heparin-bound. The ECMO blood flow was generally maintained between 80 mL/kg/min and 120 mL/kg/min. Patients underwent anticoagulation treatment with heparin to achieve an activated clotting time goal of 160—180 seconds. In patients with excessive bleeding, we lowered the goal or temporarily ceased administering the anticoagulant. We did not use aprotinin or antifibrinolytic agents during ECMO. Platelets were transfused to keep the platelet count above 50,000/mm^3, and red blood cells were generally transfused to maintain a hematocrit between 35% and 40% during ECMO use.[14]

The timing and technique of surgical repair for CDH

In our first ECMO case, we surgically repaired the CDH on the 8th day of the ECMO run and observed a tendency for bleeding during the operation. In the subsequent cases, we changed our policy to perform CDH repair early, provided that stable ECMO flow was established (usually within 72 hours of ECMO). We used a transabdominal approach for

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the CDH repair in all patients. Diaphragmatic defects were closed using nonabsorbable interrupted sutures or a polytetrafluoroethylene patch (Gore-Tex patch; W. L. Gore and Associates, Newark, DE, USA) if direct repair was impossible.

Patent ductus arteriosus ligation

If chest radiography showed persistent pulmonary congestion and echocardiography revealed a large patent ductus arteriosus (PDA) with a left-to-right shunt a few days after the surgical repair, we performed PDA ligation ($n = 4/7$ infants).

Weaning off ECMO

After surgical repair of the CDH, the decision to wean the patient off ECMO was based on the patient's cardiac and pulmonary status. Inotropic agents were then tapered. Improved lung compliance and a clear lung field on plain chest X-ray were mandatory before a trial of weaning off ECMO.

Statistical analysis

Statistical analyses were performed using the JMP version 9.0 statistical package (SAS Institute Inc., Cary, NC, USA). The Wilcoxon rank-sum test was used to compare numerical variables, and Fisher's exact test was used to compare nominal variables between the ECMO and non-ECMO patient groups. All tests were two-sided and a p value < 0.05 was considered statistically significant.

Results

Among the 39 newborns with CDH, 22 (56.4%) were male and 15 (38.5%) were premature. The demographic data are summarized in Table 1. In 27 (69%) patients, the diagnosis of CDH was based on prenatal sonography. All recorded lung–head ratios (LHRs) in this series (14 of 34 infants) were > 1. We administered antenatal steroids only for anticipated premature delivery, regardless of the LHR.

Among the 39 neonates with CDH, seven (18%) were treated using ECMO. The APGAR score at 5 minutes after birth was significantly higher in the non-ECMO group. There was no significant difference between the ECMO and non-ECMO groups in terms of gestational age, birth body weight, side of the lesion, liver herniation, and prenatal LHR. All patients in the ECMO group received HFOV and iNO for persistent pulmonary hypertension, before being placed on extracorporeal life support. In contrast, in the non-ECMO group, only 43.8% of the infants received HFOV and 9.4% of the infants received iNO. Only one (2.6%) patient had a congenital heart disease (i.e., coarctation of the aorta) other than PDA or atrial septal defect.

The pre-ECMO condition and parameters during the ECMO run are presented in Table 2. The median birth body weight was 2560 g for the ECMO-supported patient, and the lowest weight was only 1668 g. Two patients (#3 and #7) had undergone cannulae insertion and ECMO initiation in other hospitals, either by our ECMO transport team or by the referring team, and were then transported to our intensive

Table 1 Demographic characteristics of all congenital diaphragmatic hernia patients with or without ECMO support.[a]

	Total	ECMO	Non-ECMO	p
Demographics				
N (%)[a]	39 (100)	7 (17.9)	32 (82.1)	
Male[a]	22 (56.4)	3 (42.9)	19 (59.4)	0.680
GA (wks) (< 37)[b]	36.7 ± 2.0 (38.5)	35.9 ± 3.0 (57.1)	36.9 ± 1.7 (34.4)	0.359 (0.400)
BBW (g)[c]	2696 (2455–3026)	2560 (2180–3080)	2710 (2531–3024)	0.410
APGAR at 5 min[d]	7.6 ± 1.5	6.9 ± 0.9	7.8 ± 1.6	0.030*
Left side[a]	34 (87.2)	6 (85.7)	28 (87.5)	1.000
Liver up[a]	13 (34.2)	1 (14.3)	12 (38.7)	0.390
LHR[d,e]	1.78 ± 0.5	1.57 ± 0.3	1.86 ± 0.6	0.524
Patch repair[a]	8 (21.1)	1 (14.3)	7 (22.6)	1.000
HFOV[a]	21 (53.8)	7 (100)	14 (43.8)	0.010*
iNO[a]	10 (25.6)	7 (100)	3 (9.4)	<0.001*
Survanta[a]	2 (5.1)	2 (28.6)	0 (0)	0.030*
Outcome				
Survival[a]	33 (84.6)	4 (57.1)	29 (90.6)	
Days in hospital[d]	45.1 ± 50.3	99 ± 67.5	33.3 ± 37.8	0.0004*

*Indicates statistical significance.
BBW = birth body weight; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; GA = gestational age; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; IQR = interquartile range; LHR = lung–head ratio; SD = standard deviation.
[a] Data are presented as n (%).
[b] mean ± SD (%).
[c] median (IQR), or
[d] mean ± SD.
[e] Only four ECMO patients and 10 non-ECMO patients had lung–head ratio data.

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Table 2 Clinical and ECMO profiles of patients with congenital diaphragmatic hernia with ECMO support.

Patient no.	Sex	GA (wks)	BBW (g)	APGAR (1' > 5')	LHR	Pre-ECMO		ECMO run parameters	
						$AaDO_2$	OI	Age at 1st cannulation	Total bypass days
#1	F	33 + 3	2450	4 > 7	1.76	619	111	1 d	36
#2	F	31	1668	5 > 7	1.67	608	47	8 d	105
#3	M	38 + 2	3330	5 > 6	NA	631	55	< 24 h	6
#4	M	36 + 4	2560	4 > 6	1.1	603	54	< 24 h	37
#5	F	36 + 2	2180	5 > 6	NA	618	55	< 24 h	62
#6	M	37 + 2	2610	5 > 8	1.75	625	36	1 d	18
#7	F	40	3080	7 > 8	NA	603	50	2 d	5

$AaDO_2$: alveolar–arterial oxygen difference; BBW = birth body weight; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; F = female; GA = gestational age; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; LHR = lung–head ratio; M = male; OI: oxygenation index.

care unit. Six patients required extracorporeal life support within 48 hours of birth, before the surgical repair of the CDH. The other patient (#2) required ECMO support 7 days after the CDH repair. All patients received ECMO in the veno–arterial mode when undergoing their first run of ECMO. Three patients (#1, #4, and #6) required a second run of ECMO. The median total ECMO bypass times were 36 days (range, 5–105 days). The mean ECMO bypass time was significantly longer for the nonsurvivors than for the survivors (68.0 ± 34.4 days and 16.3 ± 14.4 days, respectively).

All patients who were cannulated before the hernia repair, except for the first patient, underwent surgical repair within 2 days of the initiation of ECMO. The size of the defect varied; however, only one defect was repaired by a polytetrafluoroethylene surgical patch (Gor-Tex patch; W. L. Gore and Associates). Chest tubes were inserted during the operation in four patients. The other three patients, who did not have chest tube insertion during the operation, still required chest tube insertion subsequently because of hemothorax. Five (71%) patients experienced major bleeding complications, such as hemothorax, intracranial hemorrhage, or intraventricular hemorrhage during ECMO use. The PDA was ligated in four (57.1%) patients (Table 3).

The overall survival rate was 84.6% (33/39) for all CDH patients. The survival rate was 57.1% (4/7) for the ECMO-supported patients and 90.6% (29/32) for the non-ECMO patients. In the ECMO group, one survivor (patient #6) required long-term support by bilevel positive airway pressure treatment after discharge. The other three survivors were able to breathe without ventilator support. Of the three mortalities, all were premature (gestational age, < 37 weeks). ECMO was withdrawn in two patients because they showed no improvement under prolonged support and

Table 3 Surgical repair, bleeding complications, and outcome in the ECMO group.

Patient no.	CDH repair					Bleeding complication		Outcome
	Timing of repair after cannulation	Side	Defect size (cm)	Patch repair	Chest tube Insertion	Surgical[a]	Medical[b]	
#1	8 d	L	5 × 3	N	Y	N	N	Survival to discharge
#2	−7 d[c]	L	5 × 4	N	N	Y	IVH, ICH	Severe ICH, ECMO withdrawal, expired
#3	1 d	L	NA	N	N	Y	—	Survival to discharge
#4	1 d	L	3 × 3	N	Y	N	—	Pneumonia-induced respiratory failure after weaning ECMO, expired
#5	1 d	L	6.5 × 3.5	Y	Y	Y	IVH	No recovery, ECMO withdrawal, expired
#6	2 d	L	4 × 3	N	N	Y	ICH	Discharge with long-term BiPAP
#7	1 d	R	4.5 × 4.5	N	Y	N	IVH	Survival to discharge

BiPAP = bilevel positive airway pressure; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation ICH = intracranial hemorrhage; IVH = intraventricular hemorrhage; N = no; Y = yes.

[a] Surgical bleeding is defined as hemothorax/hemopericardium on the involved side that requires chest tube (re-)insertion or reopening for hemostasis.

[b] Medical bleeding is defined as IVH or ICH, confirmed by brain echo or computed tomography.

[c] CDH repair was performed 7 days before ECMO cannulation.

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because of the development of severe complications, such as massive intracerebral hemorrhage. The other patient developed pneumonia-induced fatal respiratory failure 11 days after weaning off ECMO.

In the non-ECMO group, two of the three nonsurvivors died due to infection and unresolved pulmonary hypertension at the ages of 129 days and 224 days, respectively. The remaining patient was suspected of having had an associated tracheoesophageal fistula and could not survive at the initial resuscitation after birth. These three nonsurvivors were potential candidates for extracorporeal life support, whereas none of the surviving patients ever met the indications for ECMO.

Discussion

Survival and severity of CDH

In our experience, the survival rate among all CDH patients was 84.6%. This result was comparable to the findings of other institutions (69—93%).[2,16,17] We noted a low prevalence of comorbid major cardiac diseases in our cases [1/39 (2.6%) infants], as compared to the 10.6% prevalence reported by the Congenital Diaphragmatic Hernia Study Group (CDHSG).[18] We also noted the absence of patients with an LHR $<$ 1, which represents severe pulmonary hypoplasia, compared to 10% of patients with an LHR $<$ 1 in a Japanese study.[11]

Percentage of ECMO use

The use of ECMO in CDH neonates is widely reported in the USA.[7,8,19] According to the CDHSG report, 34% (1063/3100) of patients with CDH were managed by ECMO support between 1995 and 2004.[20] However, the frequency of ECMO use varies widely among centers, and ranges between 11% and 61%.[17] In Asia, the experience of ECMO application in neonates with CDH has not been widely reported. In a Japanese nationwide survey,[10,11] only 7% (43/614) of patients with CDH underwent ECMO between 2006 and 2010. Our frequency of ECMO use (7/39, 17.9%) is lower than that of the USA and higher than that of Japan. The latter may be due to the presence of dedicated multidisciplinary clinics for such patients, with staff trained to optimize ECMO management after a preliminary learning period.

The outcome of ECMO

Our survival rate in the ECMO group (57.1%) was comparable with other reports. For infants with isolated CDH, the reported overall survival ranged from 33—86%.[17] In the CDHSG study, the survival rate in the ECMO-supported group was 48% for the entire cohort and 61% for patients who underwent surgical repair.[20] The previous Japanese study reported a survival rate of 37.2% (16/43 patients) for CDH patients with ECMO support.[10] In the pre-ECMO era at our hospital, a study performed from 1985 to 1998 showed that CDH neonates with an oxygen index of more than 40 all died, despite HFOV support and gentle ventilation therapy.[15] In the current series, with the introduction of ECMO, we observed a survival benefit in patients with CDH who were refractory to conventional treatment. This finding is consistent with the CDHSG report that ECMO significantly improved survival in CDH neonates with a high mortality risk.[21]

In our study, the APGAR score at 5 minutes correlated significantly with the use of ECMO, while gestational age, birth body weight, and prenatal LHR did not. Our small sample size may have limited the detection of significant differences. The available literature is unfortunately insufficient to answer the question of potential correlations with other variables definitively, because of the retrospective nature of such studies. The weaknesses of available studies include unequal numbers between groups, no control for the patients' illness levels, and the use of historical controls.

Duration of ECMO

The mean duration of ECMO treatment in our study was long, especially in the nonsurvivor group (mean, 68.0 $\pm$ 34.4 days; longest duration:, 105 days). The proportion of patients in whom prolonged ECMO treatment was used (i.e., $\geq$ 21 days) was high [4/7 (57%) infants]. By comparison, in the CDHSG report, the mean ECMO bypass duration was only 9 $\pm$ 6 days for survivors and 15 $\pm$ 8 days for nonsurvivors.[20] The percentage of patients in whom prolonged ECMO support is used is generally $<$ 30%.[22] In a Japanese report, for isolated CDH patients who could survive or did not survive more than 90 days, the median duration of ECMO was 5 days (range, 1—13 days) and 8.5 days (range, 1—47 days), respectively.[10] The adequate ECMO duration for the most severe CDH remains unknown. Sufficient improvement in pulmonary function that would allow weaning a patient off ECMO could take 4 weeks or longer.[22] However, it has been noted that a longer duration of ECMO is a strong predictor of a poor outcome.[20]

In our experience, none of the CDH patients who required ECMO support for longer than 36 days survived. A similar finding was reported in a study[23] based on the Extracorporeal Life Support Organization registry data from 1998 to 2011, in which the mortality of neonates with respiratory failure who were on ECMO support for longer than 43 days was 100%. In Taiwan, the cost of ECMO for CDH has been reimbursed by the National Health Insurance scheme since 2009. The markedly prolonged use of ECMO in our patients, compared to its use in other countries, may reflect the unlimited reimbursement by the National Health Insurance. However, the unlimited duration of ECMO use does not provide a survival benefit, while it may increase health care costs and extend the suffering for the patient and the family.[24] Our longest survivor on ECMO was an adult drowning patient who experienced acute respiratory distress syndrome after hospitalization and was supported for 117 days,[25] but the pathogenesis of acute respiratory distress syndrome and of CDH differ markedly. The possibility of recovery for CDH patients is altogether worth waiting for over 6 weeks of ECMO use. However, we could not find a successful experience of neonatal respiratory failure in which ECMO support was performed for more than 6 weeks. Based on current experience, for those CDH

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patients who do not recover after 6 weeks of ECMO support, treatments other than ECMO, such as palliative care should be considered.

Complications of ECMO

Bleeding is a major complication of ECMO use, with a reported high incidence of 43% or more, and may lead to death in up to 4.8% of patients.[26] A major concern is intraoperative bleeding during CDH repair. In three of our first six patients with ECMO support, we noted a bleeding tendency during the surgery and decided to place chest tubes intraoperatively. However, the other three patients who did not undergo chest tube insertion during surgery experienced hemothorax after the operation and required bedside chest tube insertion or reoperation for hemostasis. It is widely accepted that prophylactic chest tube placement is not needed for CDH repair if there is no active bleeding.[16] A high risk of surgical site bleeding was noted in our patients on ECMO support. Severe bleeding with subsequent tension hemothorax could further lead to cardiopulmonary compromise. In this situation, emergent thoracotomy or chest tube insertion adds an extra surgical risk under systemic anticoagulation for ECMO.[27] Therefore, after our seventh patient, we routinely inserted a chest tube after the CDH repair for neonates undergoing ECMO support.

PDA ligation

The role of PDA in the management of pulmonary hypertension in patients with CDH has not been discussed previously. Left-to-right shunting through the ductus arteriosus results in pulmonary overcirculation and pulmonary edema, decreases lung compliance, and may exacerbate pulmonary hypertension. If the pulmonary edema does not improve under veno–arterial ECMO support and use of diuretics, persistent flow from the PDA is considered clinically important. However, because of the complicated disease status and multiple contributing factors, we could not observe consistent clinical improvement in our limited experience.

Timing of repair

In our first ECMO case, we performed surgical repair of CDH on the 8th day of the ECMO run and noted a bleeding tendency during the operation. In the following cases, we changed our policy to perform early CDH repair provided that a stable ECMO flow was established (usually within 72 hours of ECMO). The literature contains several reports comparing "early" and "late" repair on ECMO; it appears that patients undergoing early repair have significantly fewer complications than those undergoing late repair.[28] Regardless of the optimal timing, there remains a role for surgical repair when a patient is on ECMO. Published data are discordant since the CDHSG registry showed a statistically significant difference in the proportional hazard of death (hazard ratio = 1.41; 95% confidence interval, 1.03–1.92; p = 0.03) when comparing surgical repair on ECMO with that after ECMO decannulation.[29] Another single-center study also showed increased survival and reduced operative morbidity in patients with CDH undergoing repair after decannulation.[30] By contrast, recent reports have further complicated these data, and suggest a potential benefit to early repair (within 72 hour) on ECMO. Due to these confounding results which are based on limited data, many institutions utilize different protocols, such as weaning the patient over the course of approximately 1 week prior to surgery on ECMO or suggesting a delayed repair close to the planned decannulation date. In our institute, we prefer early surgical repair (< 72 hours) after cannulation, considering the possibility of prolonged ECMO support and the increased risk of intraoperative bleeding when the ECMO duration increases.

Study limitations

This study was based on a single-institute experience. The case number was small and our findings may only represent a preliminary learning period. Improvement and standardization of the perioperative care were not considered in the analysis.

Conclusion

In conclusion, this is the first study on the use of ECMO in neonates with CDH in Taiwan. The introduction of ECMO rescued some CDH patients who could not have survived by conventional management. However, we had no survivors after 36 days of ECMO support. We may consider routine chest tube insertion during CDH repair on ECMO support because of the high risk of postoperative bleeding.

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Please cite this article in press as: Hung W-T, et al., Extracorporeal membrane oxygenation for neonatal congenital diaphragmatic hernia: The initial single-center experience in Taiwan, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.06.012