ORIGINAL ARTICLE

Effect of Extracorporeal Membrane Oxygenation Availability on the Survival of Neonates with Congenital Diaphragmatic Hernia

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ABSTRACT

Objective: Neonatal congenital diaphragmatic hernia (CDH) is one of the major congenital anomalies with high mortality rates. Extracorporeal membrane oxygenation (ECMO) is a rescue therapy for CDH patients who do not respond to conventional ventilation strategies. The aim of this study is to compare the epochs before and after the introduction of neonatal ECMO program and to determine its impact on response and survival of neonates with isolated CDH. **Materials and Methods:** Admitted neonates with CDH patients since 2012 were separated into two epochs according to the establishment of ECMO: Pre-ECMO period (January 2012–August 2015) and ECMO period (September 2015–December 2017). The demographic, clinical, and surgical data of the patients were compared between these two periods. **Results:** During the study period, a total of 35 neonates with CDH were admitted. Patient characteristics and surgical data were similar in both groups. Need for high-frequency oscillatory ventilation (HFOV) was higher in the pre-ECMO period ($P = 0.04$). The length of hospitalization was longer in ECMO period ($P = 0.01$). Three among seven patients who received ECMO survived (43%). Survival rates at the time of discharge were similar in groups (39% vs. 47%, $P = 0.625$). It was demonstrated that having oxygenation index >40 at first 24 h (odds ratio (OR): 12, 95% Cl 2.37–60.64, $P = 0.03$) and the ratio of pulmonary artery pressure to systolic pressure > 1 (OR: 6, 95% Cl 1.33–27.04, $P = 0.02$) increased mortality. **Conclusion:** The establishment of neonatal ECMO program was not associated with an improvement in survival of isolated CDH patients. We suggest that better outcomes may be achieved with defining selective criteria for ECMO candidates.

Key words: Congenital diaphragmatic hernia; Extracorporeal membrane oxygenation; Neonate; Survival

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is one of the major congenital anomalies with an incidence of 1 in 2500–3000 live births [1,2]. Despite advances in neonatal care and intensive efforts to improve outcomes for infants with CDH, the mortality remains high at approximately 30–40% [3-5]. Supportive treatments as inhaled nitric oxide (iNO), high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO) followed by surgical repair after stabilization are the postnatal managements. The stabilization period focuses on gentle ventilation strategies and aggressive treatment of pulmonary hypertension [6,7].

ECMO is a rescue therapy for CDH patients who do not respond to conventional treatment modalities such as HFOV and iNO [8,9]. The first use of ECMO was reported by German et al. in 1977 in four CDH patients, of whom only one survived [10]. CDH has become the most common non-cardiac indication for ECMO [11,12]. Extracorporeal life support organization reports 50% survival for CDH patients which has not improved over the past few decades and remains same [13].

Our center is the first and the only center that performs ECMO in the neonatal intensive care unit (NICU) for newborns with respiratory or cardiac failure in Turkey. We decided to analyze the periods before and

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after the introduction of the neonatal ECMO program which has been started at September 2015 in our unit and to determine its impact on survival and progress of CDH patients.

MATERIALS AND METHODS

The present study represents a before and after retrospective cohort study of neonates with CDH who were treated at our NICU between January 2012 and December 2017. The study was approved by the local ethics committee. The ECMO program has been established in our NICU since September 2015. All newborns with CDH admitted to our NICU in the past 6 years were divided into two groups: Pre-ECMO period (January 2012–August 2015) and ECMO period (September 2015–December 2017). The demographic, clinical, and surgical data of the patients were compared between groups.

Management of patients

All patients were followed according to CDH Euro Consortium guideline which was published at 2010 and revised at 2015 [14,15]. The infants who had antenatal diagnosis of CDH intubated in the delivery room if presented with respiratory distress and stabilized with conventional mechanical ventilation. The lung protective strategy, using conventional mechanical ventilation as the initial ventilation support aiming for pre-ductal saturation between 80% and 95% and post-ductal saturation above 70%, was adopted. HFOV was considered if mean airway pressure (MAP) was ≥15 cm H_2O, and need of FiO_2 was >0.80. The oxygenation index (OI) was calculated in every 4 h for all infants (OI: [MAP × FiO_2/ Post-ductal PaO_2] × 100).

A nasogastric tube for gastric decompression and urinary catheter for urine output monitoring were inserted. Hemodynamic support was accomplished with various combinations of inotropic agents.

All infants underwent echocardiographic evaluation on admission to access pulmonary artery pressure and rule out cardiovascular malformations. The ratio of estimated pulmonary artery pressure to systemic pressure (PSR) was calculated to evaluate the pulmonary hypertension severity [16]. iNO was administered at a dose of 20 ppm in cases of pulmonary hypertension with pre-ductal and post-ductal saturation difference >10% and confirmed by echocardiography.

Surgical repair of the defect was undertaken once cardiovascular stability was achieved generally beyond the 1st day of life. The timing for repair was judged in conjunction with the NICU team and pediatric surgeons if the patient has pre-ductal oxygen saturation between 85% and 95%, normal mean blood pressure for gestational age (GA), lactate <3 mmol/L, urine output >1 mL/ kg/h, and an estimated pulmonary artery pressure less than systemic pressure.

ECMO treatment

A neonate with CDH was considered to receive ECMO before or after the surgical repair if he/she has the following criteria as (a) OI >40 for 4 h, (b) severe hypoxic respiratory failure with acute decompensation (PaO_2 <40 mmHg), (c) progressive respiratory failure and/or pulmonary hypertension with evidence of right ventricular dysfunction or continued high inotropic requirement, and (d) inability to maintain pre-ductal saturation >85% despite optimal ventilation and management of pulmonary hypertension [17]. Infants with GA <34 weeks, body weight ≤2000 g, uncontrolled bleeding disorder, or irreversible brain damage were not accepted as a candidate for the ECMO.

Once the patient was stabilized on ECMO before surgery, the CDH repair was preferred to perform at the earliest time when possible. If the patient was not stabilized after surgery with conventional treatment, ECMO cannulation was decided.

The patients were cannulated for ECMO in our institution by pediatric cardiovascular surgeons. Venovenous (VV) ECMO was preferred in CDH patients, whereas venoarterial (VA) ECMO was essentially reserved for infants who cannot be cannulated for VV ECMO due to cannula versus vessel size incompatibility or who have cardiovascular instability. We applied ECMO with centrifugal pumps (Maquet Rotaflow, Maquet Cardiopulmonary AG, Hirrlingen, Germany) and hollow-fiber membrane oxygenators (Maquet Quadrox-iD, Maquet Cardiopulmonary AG, Hirrlingen, Germany). The usual practice is to start with a pump flow of 100– 150 mL/ kg/min. Patients received continuous heparin infusion (20–50 units/kg/min) to keep activated clotting time level around 160–220 s. The blood components were transfused if hematocrit level < 35%, platelet count <100.000/mm³, and fibrinogen <1.5 g/L during the ECMO run. With the improvement of the underlying disease and the clinical condition, patients were weaned from ECMO by slowing down the pump flow. During weaning process, ventilator support was escalated, and inotrope support was started if necessary. Decannulation was anticipated by pediatric cardiovascular surgeons.

Statistical analysis

The data were analyzed with SPSS for Windows 15 (SPSS, Chicago, IL). Clinical and demographic characteristics of the patients in the period under study were compared using the Student *t*-test and analysis of variance for continuous variables. Categorical variables were compared using Chi-square test, and if
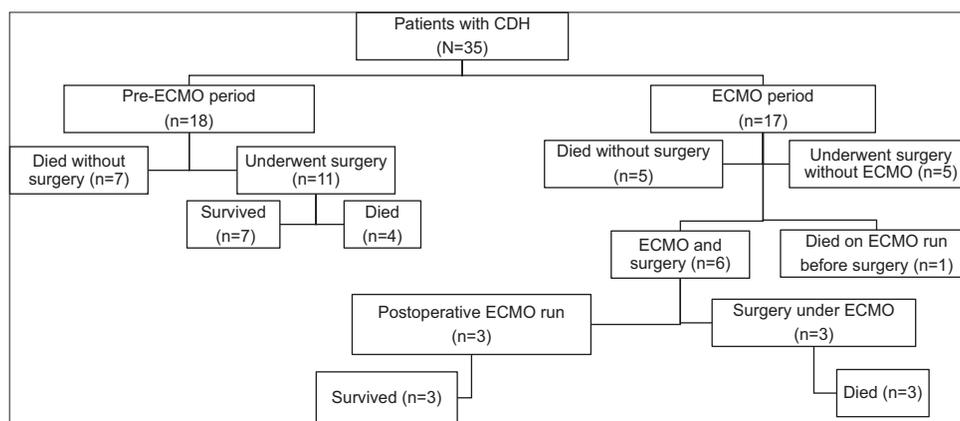
Figure 1: Patients with congenital diaphragmatic hernia who were admitted to our neonatal intensive care unit during the study periods. CDH: Congenital diaphragmatic hernia, ECMO: Extracorporeal membrane oxygenation

the expected number of observations was <5, Fisher's exact test was used; a $P < 0.05$ was considered statistically significant. Multiple logistic regression analyses were performed to identify factors associated with mortality.

RESULTS

Thirty-five neonates, of whom 18 from the pre-ECMO and 17 from the ECMO period, were enrolled in the study (Figure 1). There was no significant difference in patient characteristics with respect to GA (38 ± 1.8 w vs. 38.4 ± 1.6 w, $P = 0.42$), birth weight (BW) (2910 ± 546 g vs. 3030 ± 782 g, $P = 0.6$), gender (male) (83% vs. 65%, $P = 0.26$), antenatal diagnosis rate (72% vs. 71%, $P = 1.0$), APGAR score at 5 min, side of lesion, and liver or stomach herniation. The highest OI and PSR of patients in the first 24 h, in addition to iNO and surfactant use rates, were similar between the groups ($P > 0.05$). The need for HFOV was higher in patients in pre-ECMO period (89% vs. 59%, $P = 0.04$), whereas the length of hospitalization was longer in ECMO period (7.7 ± 7.4 day vs. 18.2 ± 15.6 day, $P = 0.01$) (Table 1).

All patients except one who was transferred postoperatively were operated in our center by the same pediatric surgery team. During the pre-ECMO period, 61% (11/18) of the patients underwent surgery at a mean age of 2.8 ± 1.6 days, whereas 39% (7/18) never achieved the required stability to qualify for surgery. 11 of 17 infants (65%) underwent surgery during the ECMO period at a mean age of 4 ± 2.5 days, whereas six infants (35%) could not be stabilized for the operation in this period. Two of six infants could not be cannulated for ECMO due to the absence of appropriate cannula size for their low BW.

The findings of patients who received ECMO run are shown in Table 2. Seven of the 17 (41%) patients received ECMO support. The mean duration of ECMO run was 12.3 ± 3.8 days, and 57% was VA ECMO. Patients with CDH who received ECMO before or

after surgery were all left-sided. Three of seven (43%) infants had transabdominal repair during ECMO run, and none of them survived. Three infants (43%) received ECMO after surgery, and all of them survived. The remaining one patient was supported with ECMO before surgery but could not be operated, and ECMO run was withdrawn on 13th day of his life due to severe brain injury.

The overall survival rate of all CDH patients during the study period was 43% (15/35). Survival rates at the time of discharge were similar as 39% (7/18) in pre-ECMO period versus 47% (8/17) in the ECMO period ($P = 0.625$). The influences of demographic and clinical parameters on mortality were evaluated in all CDH patients ($P = 35$) during the study period. Logistic regression analysis demonstrated that having OI >40 at first 24 h (odds ratio [OR]: 12, 95% Cl 2.37-60.64, $P = 0.03$) and PSR >1 (OR: 6, 95% Cl 1.33–27.04, $P = 0.02$) increased the mortality rate.

DISCUSSION

CDH is a condition that is associated with high mortality rates, despite advances both in prenatal and neonatal cares [4,5]. The role of ECMO in the treatment algorithms of CDH remains controversial, and there are no universally accepted criteria for the initiation of ECMO in neonates with CDH. In non-randomised studies suggest that introduction of ECMO improved the survival in CDH patients; however, the meta-analysis of randomized trials reported a reduction in early mortality but no long-term benefit with ECMO treatment. A Cochrane review concluded that the benefit of ECMO for neonates with CDH is unclear [18-20].

We could not find an improvement in survival of CDH patients when compared the periods before and after the establishment of neonatal ECMO program. Although the patient profile was similar for both periods, the use of HFOV was higher in pre-ECMO period. 69% of patients who needed HFOV did not survive in this period, which

Table 1: The demographic and clinical data of patients in both groups

Parameter	Pre-ECMO period (n=18)	ECMO period (n=17)	P value
Gestational age, (w)*	38±1.8	38.4±1.6	0.42
Birth weight, (g)*	2910±546	3030±782	0.60
Gender (male), n (%)	15 (83)	11 (65)	0.26
APGAR 5' min**	7.5 (1-9)	7 (4-9)	0.88
Prenatal diagnosis, n (%)	13 (72)	12 (71)	1.0
Left CDH, n (%)	18 (100)	16 (94)	0.48
Liver hernia, n (%)	11 (61)	8 (47)	0.73
Stomach hernia, n (%)	13 (72)	10 (59)	1.0
OI*	36.5±24.4	37.2±20.7	0.91
OI>40, n (%)	7 (39)	11 (65)	0.18
PSR*	1.1±0.4	1.2±0.3	0.43
HFOV use, n (%)	16 (89)	10 (59)	0.04
iNO use, n (%)	6 (33)	10 (59)	0.18
Surfactant use, n (%)	12 (67)	7 (41)	0.18
Underwent surgery, n (%)	11 (61)	11 (65)	1.0
Operation day, (d)*	2.8±1.6	4±2.5	0.2
Patch use in operation, n (%)	2 (18)	2 (45)	0.17
ECMO, n (%)	-	7 (41)	NA
Length of hospitalization, (d)*	7.7±7.4	18.2±15.6	0.01
Survival, n (%)	7 (39)	8 (47)	0.62

*Data given as mean±SD, **Data given as median. ECMO: Extracorporeal membrane oxygenation, HFOV: High-frequency oscillatory ventilation, iNO: Inhaled nitric oxide, OI: Oxygenation index, PSR: Ratio of pulmonary arter pressure to systolic pressure, CDH: Congenital diaphragmatic hernia

led us to think that they were candidates for ECMO and might have a chance to survive, if ECMO was available. The hospitalization day of patients was longer in ECMO period ($P = 0.01$), which may be associated with the duration of ECMO run.

The optimal timing for CDH surgical repair is difficult to determine. Although no clear evidence exists favoring delayed surgery in CDH, surgical strategies have shifted from early repair to delayed repair after pre-operative hemodynamic stabilization [21-24]. Surgical repair is performed in nearly 80% of infants with CDH at a mean age of 7 days after stability is improved [25,26]. For those patients not requiring ECMO, repair is usually offered no sooner than 48–72 h after birth [27]. In our CDH series,

the mean age at operation was 3.4 ± 2 days during the study period which was not found to be associated with mortality. The decision of surgery is more difficult, if the patient is on ECMO run. Several studies suggested that, if decannulation could be achieved before surgery, the survival was improved [26,28-30]. Surgical repair on ECMO run is associated with a higher incidence of bleeding [26,29]. There is an increasing consensus that repair at an early stage (within 2 weeks) of ECMO may help with either weaning period or decision on withdrawal and improve the outcome [29]. The survival rate of our CDH patients treated with ECMO was 43% (3/7). All patients (3/3) who required ECMO after surgery (at mean age of 2 days) survived. Three patients who were operated at a median age of 7 days while ECMO run did

Table 2: The features of congenital diaphragmatic hernia patients treated with ECMO

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gestational age, (week)	39.4	40	36.4	41	41.2	38.6	38.5
Birth weight, (g)	3185	3650	2780	3310	4200	3500	2850
Gender	F	M	F	M	M	F	M
APGAR 5' min	8	8	8	5	9	7	7
Mode of delivery	CS	NVD	CS	NVD	CS	CS	CS
Birth place	Inborn	Outborn	Inborn	Outborn	Outborn	Inborn	Outborn
Age at admission, (days)	1	1	1	1	12	1	1
Ventilation day before ECMO	3	2	7	3	11	3	2
Age at ECMO placement (days)	3	2	7	3	12	3	2
OI before ECMO	43	58	44	44	52	48	46
A-a gradient before ECMO	592	450	720	520	700	580	560
ECMO type	VV	VA	VA	VA	VV	VV	VA
Duration of ECMO, (days)	6	8	16	13	14	14	15
Time of repair regard to ECMO	Under	Under	Before	Not operated	Before	Before	Under
Age at surgery (days)	9	8	2	-	2	2	8
Length of hospitalization, (days)	12	20	38	14	28	47	17
Survival to discharge	Exitus	Exitus	Discharged	Exitus	Discharged	Discharged	Exitus

F: Female, M: Male, CS: Cesarean section, NVD: Normal vaginal delivery, ECMO: Extracorporeal membrane oxygenation, OI: Oxygenation index, VV: Venovenous, VA: Venoarterial

not survive. This may be explained by the fact that the most severe CDH cases received ECMO. Further studies are needed to consider the timing of ECMO in which CDH patients are most likely benefit.

Our study had few limitations as including a single-center experience with a retrospective data collection and a small number of cases, but it reflects the initial ECMO experience of the first and the only referral center in our country.

CONCLUSION

CDH remains a clinical challenge with high rates of morbidity and mortality. The establishment of neonatal ECMO program was not associated with an improvement in survival of CDH patients in our study. It is still difficult to determine the optimal timing of CDH repair, optimal patient selection for ECMO in CDH, and timing of repair once ECMO is commenced. We suggest that better outcomes may be achieved with defining selective criteria for ECMO run in CDH patients.

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