

# Extracorporeal Membrane Oxygenation for Congenital Diaphragmatic Hernia: A Single Center Experience in Turkey

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## ABSTRACT

**Objective:** Extracorporeal membrane oxygenation is a temporary life-support modality offered for stabilizing neonates with congenital diaphragmatic hernia who are in a critical condition and unresponsive to optimal medical therapy. The aim of this study was to examine our institutional outcomes of early congenital diaphragmatic hernia repair on extracorporeal membrane oxygenation.

**Materials and Methods:** A total of 17 extracorporeal membrane oxygenation-supported patients with congenital diaphragmatic hernia were evaluated and the demographic, diagnostic, laboratory, clinical data, complications and outcome of the patients were reported.

**Results:** The study consisted of 7 females and 10 males. Mean birth weight was 3107 g (range, 2360–3840 g). Median age of extracorporeal membrane oxygenation initiation was 2.1 days. In total four patients received venovenous extracorporeal membrane oxygenation. Other patients received venoarterial extracorporeal membrane oxygenation via aortic and right atrial cannulation. The mean duration of extracorporeal membrane oxygenation was 25 days (range: 1-140 days). Six patients (35.2%) could be weaned from extracorporeal membrane oxygenation. The most common extracorporeal membrane oxygenation related complications were hemorrhage, disseminated intravascular coagulation and limb ischemia (64.7%, 41.1% and 29.4%, respectively). Diaphragmatic defect was repaired via a subcostal incision in 12 of 13 patients. In 88.2% of patients diaphragmatic repair was performed with polytetrafluoroethylene patch. In 77% of patients early congenital diaphragmatic hernia repair was performed concomitantly with extracorporeal membrane oxygenation insertion. The survival rate was 17.6%.

**Conclusion:** Early repair of congenital diaphragmatic hernia in neonates on extracorporeal membrane oxygenation can be associated with high rates of morbidity and mortality. However, extracorporeal membrane oxygenation may be considered a life-saving measure for patients with congenital diaphragmatic hernia who would have otherwise not been salvageable.

**Keywords:** Congenital diaphragmatic hernia, extracorporeal membrane oxygenation, newborn, surgery

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## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a severe and complex congenital anomaly occurs approximately 1 in every 2500 to 3000 live births [1]. Despite the advances in medical and surgical techniques

and neonatal care capabilities overall survival rate for CDH is still high. Both pulmonary hypoplasia and persistent pulmonary hypertension are considered to be the principal factors determining the survival.

Consequently, a considerable amount of neonates with CDH and persistent pulmonary hypertension may necessitate additional support to provide sufficient tissue oxygenation and perfusion [2, 3]. In such patients who have unstable hemodynamic parameters and low saturations despite optimal medical management and ventilation support, extracorporeal membrane oxygenation (ECMO), which is a temporary and modified form of cardiopulmonary bypass, should be considered as a bridging strategy until patient stabilization [4, 5].

Although management with ECMO has been proven to be associated with better overall survival in patients with CDH, it carries a mortality rate reaching up to 50% primarily due to the systemic anticoagulation-related risk of bleeding [6-8].

Most reports regarding the use of ECMO in CDH neonates are from the USA. There are fewer papers reported in Asia and Europe [9-11]. In recent years, the use of ECMO reported in Turkey has been involving adult patients primarily. Despite pediatric ECMO applications have been increasing in Turkey, there is only one study mentioning the use of ECMO in CDH to our knowledge [12]. The purpose of our study is to report our experience with the use of ECMO in CDH patients and its outcomes. We are not aware of any previous report emphasizing the results of ECMO usage in patients with CDH in Turkey.

## MATERIALS and METHODS

Data of 17 neonates who were operated for CDH were analyzed. In addition to patient characteristics, data were collected including the following variables: Associated cardiac comorbidity, results of preoperative arterial blood gas analysis, right ventricular systolic pressure values, ventilator management, ECMO timing, cannulation site, duration, and complications, surgical technique preference for hernia repair, application of post ECMO stem-cell therapy and in-hospital mortality. Survival status

was determined from the date of the last follow-up. The neonates were admitted to the neonatal intensive care unit after delivery. Patients with hemodynamic compromise and respiratory distress were stabilized using usual medical therapy and ventilation support. Indication for ECMO in CDH patients was failure of conventional medical management strategies. Patients with life-threatening congenital anomalies, uncontrolled bleeding, and irreversible brain damage were excluded.

ECMO cannulations were performed by pediatric cardiovascular surgeons in the operation room. Hernia repair was performed by pediatric surgeons either concomitantly with or several days after the ECMO cannulation. In our institution, the preferred ECMO strategy and cannulation method for neonates with CDH were venoarterial (VA) ECMO and central cannulation through the ascending aorta and right atrium, respectively. The ECMO circuit included a centrifugal pump and a hollow-fiber membrane oxygenator with an integrated heat exchanger.

Statistical analysis was performed using SPSS 21 for Windows (SPSS Inc., Chicago, IL, USA). The demographic and clinical findings of the patients were described with rates and percentages, mean, and median values.

## RESULTS

The study consisted of 7 females and 10 males. Mean birth weight (BW) was 3107 g (range, 2360–3840 g). CDH was left sided in 88% of patients. Mean right ventricular systolic pressure was calculated as 63.8 mmHg (range, 35–85 mmHg). The basic demographic data are summarized in Table 1. Measurements of pH, PCO<sub>2</sub>, PO<sub>2</sub> and oxygen saturation values in arterial blood analysis before initiation of ECMO were  $7.13 \pm 0.19$ ,  $67.47 \pm 26.9$ ,  $47.9 \pm 23.2$  and  $76.46 \pm 11.9$ , respectively.

Table 1. Patient characteristics and demographic data.

Patient no	Sex	BBW (g)	CDH side	Additional cardiac anomalies	RV systolic pressure (mmHg)
#1	F	3260	Left	ASD, PDA, TR	70
#2	M	3200	Left	ASD, PDA, TR, MR	70
#3	F	3840	Left	TR	68
#4	F	3500	Left	ASD, PDA	60
#5	F	3540	Right	ASD, PDA	75
#6	M	2360	Left	PDA	80
#7	F	2580	Left	MR	50
#8	M	3180	Left	TR, MR	70
#9	F	3160	Left	PDA	55
#10	M	3200	Left	PDA	-
#11	F	2580	Left	PDA	50
#12	M	3250	Left	PDA	-
#13	M	2720	Right	ASD, PDA	85
#14	M	3000	Left	MR	35
#15	M	3470	Left	PDA, TR	70
#16	M	3220	Left	PDA, TR	55
#17	M	2760	Left	PDA, MR	65

F: Female; M: Male; BBW: Birth body weight; CDH: Congenital diaphragmatic hernia; ASD: Atrial septal defect; PDA: Patent ductus arteriosus; TR: Tricuspid regurgitation; MR: Mitral regurgitation RV: Right ventricle

Table 2 summarizes the details of ECMO run. Median day of ECMO initiation was 2.1 (1-8). Two patients received direct venovenous (VV) (Patients 6 and 16) and the others received VA ECMO via aortic and right atrial cannulation. In two patients (Patients 15 and 17) VA ECMO support was converted to VV due to stable hemodynamic outcome. The mean

duration of ECMO was 25 days (range: 1-140 days). Six patients (35.2%) could be weaned from ECMO. The most common ECMO related complications were hemorrhage, disseminated intravascular coagulation (DIC) and limb ischemia (64.7%, 41.1% and 29.4%, respectively).

Table 2. Details of ECMO run.

Patient no	Timing (d)	Cannulation site	Days on ECMO	Complication	Survived ECMO	Survived to DC
#1	2 <sup>nd</sup>	Ao-RA	74	DIC, hemorrhage, HIT	+	+
#2	3 <sup>rd</sup>	Ao-RA	15	Sepsis, hemorrhage, MOF	-	-
#3	1 <sup>st</sup>	Ao-RA	140	Limb ischemia, HIT, DIC	+	-
#4	8 <sup>th</sup>	Ao-RA	8	-	+	+
#5	1 <sup>st</sup>	Ao-RA	12	Hemorrhage, sepsis	-	-
#6	1 <sup>st</sup>	Bi-caval dual lumen	1	Hemorrhage, pericardial tamponade	-	-
#7	1 <sup>st</sup>	Ao-RA	8	DIC, MOF, low output	-	-
#8	1 <sup>st</sup>	Ao-RA	42	Limb ischemia, MOF, hemorrhage	-	-
#9	4 <sup>th</sup>	Ao-RA	4	DIC, hemorrhage	-	-
#10	2 <sup>nd</sup>	Ao-RA	13	Limb ischemia, hemorrhage, low output	-	-
#11	1 <sup>st</sup>	Ao-RA	1	Limb ischemia, hemorrhage	-	-
#12	1 <sup>st</sup>	Ao-RA	29	Limb ischemia, hemorrhage, MOF	-	-
#13	1 <sup>st</sup>	Ao-RA	2	Hemorrhage, low output	-	-
#14	1 <sup>st</sup>	Ao-RA	3	SIRS	-	-
#15*	3 <sup>rd</sup>	Ao-RA/ Bi-caval dual lumen	26/4	Capillary leak, DIC	+	+
#16	4 <sup>th</sup>	Bi-caval dual lumen	25	Hemorrhage, DIC	+	-
#17*	2 <sup>nd</sup>	Ao-RA/ Bi-caval dual lumen	22/16	DIC, sepsis	+	-

V: Venous; Ao: Aorta; RA: Right atrium; ECMO: Extracorporeal Membrane Oxygenation; HIT: Heparin induced thrombocytopenia; DIC: Disseminated intravascular coagulation, MOF: Multi-organ failure, SIRS: Systemic inflammatory response syndrome

\* ECMO strategy was converted from Ao-RA VA to bicaval venovenous.

Diaphragmatic defect was repaired via a subcostal incision in 12 out of 13 patients. In 88.2% of patients diaphragmatic repair was performed with polytetrafluoroethylene surgical patch (Gore-Tex® patch; W. L. Gore and Associates). Two patients received primary closure of the diaphragm. In 77% of patients early CDH repair was performed concomitantly with ECMO insertion. The repair was delayed until the 5th day of ECMO run in three patients (Patients 8, 10 and 17). We were unable to perform

the repair in four patients due to severe cardiac tamponade which leads to sudden cardiac death (Patient 6), severe disseminated intravascular coagulation (Patients 9 and 13) and severe sepsis (Patient 14). Seventy-six percent of patients received continuous venovenous hemodiafiltration (CVVHDF) and/or plasma exchange (PE) during ECMO run. The survival rate was 17.6% (Patients 1, 4 and 15). Details of surgical repair, additional therapies, and outcome of patients are summarized in Table 3.

Table 3. Surgical repair, additional therapies, and outcome.

Patient no.	Repair incision	Repair time (d)	Additional ventilation support	CVVHDF and/or PE	Stem-cell Therapy
#1	Median sternotomy	Early	HFOV	CVVHDF	+
#2	Subcostal	Early	-	CVVHDF	-
#3	Subcostal	Early	HFOV	CVVHDF, PE	+
#4	Subcostal	Early	HFOV	-	-
#5	Subcostal	Early	-	CVVHDF, PE	-
#6	-	-	-	-	-
#7	Subcostal	Early	HFOV	CVVHDF	-
#8	Subcostal	Late	HFOV	CVVHDF, PE	+
#9	-	-	-	PE	-
#10	Subcostal	Late	-	CVVHDF, PE	+
#11	Subcostal	Early	HFOV	-	-
#12	Subcostal	Early	HFOV	-	+
#13	-	-	HFOV	CVVHDF	-
#14	-	-	HFOV	CVVHDF	-
#15	Subcostal	Early	HFOV	CVVHDF	-
#16	Subcostal	Early	-	-	-
#17	Subcostal	Late	HFOV	CVVHDF	+

HFOV: high frequency oscillatory ventilation, CVVHDF: continuous venovenous hemodiafiltration, PE: plasma exchange

## DISCUSSION

CDH is a developmental failure of the diaphragm due to incomplete fusion of elements structuring the diaphragm. It occurs most frequently in the left side and associated with the herniation of the abdominal viscera into the chest cavity. Decreased surface area of the alveoli and the vascular bed (lung hypoplasia), the development of the abnormal pulmonary vasculature, which is more prone to developing resistance and activation of thromboxane

synthetase pathways lead to persistent pulmonary hypertension and respiratory failure, subsequently [5, 13, 14]. Management of the respiratory failure in CDH is complicated and includes both ventilation and pharmacological methods. The initiation of high-frequency oscillatory ventilation (HFOV), is pivotal. Inhaled nitric oxide (iNO) and administration of surfactant may improve oxygenation. Parallel to the advancements of these strategies worldwide uses of

ECMO for neonatal acute hypoxic respiratory failure reduced in the last decades [15-17]. Nevertheless, ECMO is considered the only intervention for infants who continue to demonstrate respiratory or cardiac failure despite optimal medical and/or ventilation support [18].

The first successful use of ECMO in a newborn with cardiopulmonary failure was reported by Bartlett et al. in 1975 [19]. Nowadays, the frequency of ECMO usage for CDH ranges between 0% to 61%, with mortality rates of 30% to 40% [2, 18, 20]. Although ECMO can be a life-saving intervention and improves survival in newborns with CDH, it embraces substantial complications including major bleeding, intracranial infarct or bleed, seizures, and infection. The rate of these complications increase primarily with prolonged ECMO usage and relevant mortality may reach up to 50% [5, 21]. Thus, it is critical to give the decision of ECMO initiation with a multidisciplinary approach. In our study, the decision for all ECMO initiations was made by a multidisciplinary approach with the primary initiative of the intensive care physicians. The optimal timing of repair of diaphragmatic hernia of patients on ECMO is difficult. In 10 patients, diaphragmatic hernia was repaired during the operation for ECMO cannulation. Three patients had surgical repair of hernia on 5th day of ECMO run. Diaphragmatic hernia repair while on ECMO was preferred to restore normal anatomy and prevent complications such as intestinal ischemia and volvulus. Furthermore, to decrease the mechanical compression on lungs and pulmonary circulation may improve respiratory functions earlier. On the other hand, surgical repair of hernia while on ECMO may lead complications associated with bleeding which can be lessened by anticoagulation treatment and tranexamic acid. None of our patients had bleeding during hernia repair.

There are very few randomized studies regarding the use of ECMO in CDH in the literature and the results are debatable. Survival benefit of ECMO in CDH could not be demonstrated in a study from the UK. In addition, a meta-analysis of randomized trials was unable to state a survival advantage of ECMO usage in CDH when compared with neonates managed

without ECMO support. Besides, according to the Cochrane review of the randomized studies the advantage of ECMO usage in CDH is debatable [22-24]. Nevertheless, Garcia et al. emphasize ECMO usage in carefully selected patients with CDH for reversible respiratory disease as a strategy to minimize further barotrauma [25]. Mortality rate was considerably high in our study (82.4%). DIC, hemorrhage and sepsis, which all are associated with ECMO usage, were the potential causes of mortality. Besides, the average duration of ECMO run (25 days) is high in the present study which undoubtedly plays a role in adverse outcomes and complications. In the light of these results, we think that ECMO usage in patients with CDH is debatable. Estimation of overall outcome is very difficult due to variations of individual responses. Thus, the decision of ECMO initiation should be individualized and considered primarily based on the reversibility of the respiratory problem. We also believe that survival rate could be increased with growing experience, advancements in ECMO technology and application of novel tissue engineering strategies such as stem cell therapy.

#### **LIMITATIONS OF THE STUDY**

This is a retrospective study based on a single-institute experience. The study population is very small and there is no control group. Thus, our findings may only reflect the preliminary results of a learning period.

#### **CONCLUSION**

ECMO has high morbidity and mortality rates in neonates with CDH and its survival benefit is unclear. Therefore, further prospective studies with larger patient samples are warranted to evaluate its applicability in patients with CDH. In the meantime, ECMO may be considered a life-saving measure for patients with CDH who would have otherwise not been salvageable.

#### **CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.



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