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Congenital diaphragmatic hernia: to repair on or off extracorporeal membrane oxygenation?

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Abstract

Background: Congenital diaphragmatic hernia (CDH) can be repaired on or off extracorporeal membrane oxygenation (ECMO). In many centers, operating off ECMO is advocated to prevent bleeding complications. We aimed to compare surgery-related bleeding complications between repair on or off ECMO.

Methods: All patients with CDH repair and ECMO treatment between January 1, 1995, and May 31, 2008, were retrospectively reviewed. Tranexamic acid was routinely given to all patients repaired on ECMO for 24 hours perioperatively after 2003. Extra-fluid expansion, transfusion, or relaparotomy caused by postoperative bleeding were scored as surgery-related bleeding complications and were related to the Extracorporeal Life Support Organization (ELSO) registry. We used χ^2 test and t test for statistics.

Results: Demographic data and surgery-related bleeding complications in the on-ECMO group were not significantly different compared with the off-ECMO group ($P = .331$) in our institute. In contrast, more surgery-related bleeding complications were reported by ELSO in their on-ECMO group ($P < .0001$).

Conclusion: In contrast to the data from the ELSO registry, we did not observe significantly more surgery-related bleeding complications after CDH repair on ECMO. Using a specific perioperative hemostatic treatment enabled us to perform CDH repair on ECMO with a low frequency of bleeding complications, thereby taking advantage of having the physiologic benefits of ECMO available perioperatively.

Congenital diaphragmatic hernia (CDH) is a developmental defect in the diaphragm resulting in herniation of the abdominal viscera into the thorax. The incidence of CDH is approximately 1 in 2200 live births. The primary determinants of mortality in patients with CDH are the degree of associated pulmonary hypoplasia (PH) and persistent pulmonary hypertension (PPH) (reviewed in Sluiter et al [1]). The treatment of CDH consists of preoperative stabilization

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directed toward optimal management of PH and PPH, followed by surgical repair of the diaphragmatic defect either primarily or with a patch [2].

Treatment of CDH remains a challenge for both pediatric surgeons and pediatric intensive care specialists. Survival of these children has improved substantially during the past decades. Better antenatal diagnosis and advances in neonatal intensive care after the introduction of gentle ventilation strategies are responsible for this improvement [3].

One of the treatment modalities for CDH in the neonatal period is extracorporeal membrane oxygenation (ECMO); ECMO provides a temporary cardiopulmonary bypass system to overcome reversible lung failure. Respiratory failure may be attributed to PPH and/or PH that is associated with CDH [3-5]. Survival rates for patients with CDH undergoing ECMO treatment currently range from 44% to 86% [6]. Extracorporeal membrane oxygenation has been available in our institution since 1993. Indications for ECMO treatment of babies with CDH in our institution are failure of maximal conventional therapy and fulfillment of strict ECMO criteria predicting an 80% mortality, as published previously [7]. Different criteria, however, exist between institutions with respect to when to initiate ECMO treatment [8,9].

In 2002, the CDH study group reported that 54% of infants with CDH placed on ECMO underwent repair of the diaphragmatic defect while on ECMO [8]. Timing of CDH repair in patients requiring ECMO remains controversial and is dependent on local protocols [6]. One of the reasons to operate subsequent to ECMO treatment is the concern of surgery-related bleeding complications. Hemorrhage, in general, is a major complication in neonates on ECMO [8].

The aim of our study was to determine the number of surgery-related bleeding complications in patients undergoing CDH repair on ECMO and to compare this number with those undergoing CDH repair off ECMO in our institution. We were able to perform this study because we initially started CDH repair after ECMO treatment but switched to CDH repair while on ECMO after establishing a new protocol to prevent bleeding complications in 2003. We observed no significant differences in surgery-related bleeding complications between the on-ECMO and off-ECMO CDH repair groups in our institution. Subsequently, we compared these results with those of the Extracorporeal Life Support Organization registry (ELSO registry) and found that there were a significantly higher number of surgery-related bleeding complications in the on-ECMO CDH repair group in the ELSO registry.

1. Materials and methods

1.1. Eligibility criteria

We retrospectively reviewed all charts of patients undergoing open abdominal CDH repair while on ECMO or after ECMO treatment in our institution between January 1, 1995, and May 31, 2008.

1.2. Surgery

During this study period, all patients underwent open operative CDH repair, and all surgeons used a subcostal incision. Diaphragmatic defects were closed using either nonabsorbable interrupted sutures or a Goretex patch (W. L. Gore & Associates, Inc., Flagstaff, AZ), according to the choice of the attending surgeon. All patients undergoing repair on ECMO were operated on in the intensive care unit (ICU), whereas off-ECMO patients underwent repair in the operating room.

1.3. ECMO protocol in our institute

During the study period, the same circuit, type of tubing, and roller pump were used in all patients. Hemolysis was evaluated on a daily basis as discussed later in more detail. Since 2003, all patients in our institute are treated with tranexamic acid (TEA; Cyklokapron; Pfizer, Capelle a/d Ijssel, The Netherlands) perioperatively until 24 hours postoperatively. In detail, a loading dose (4 mg/kg) is given 1 hour before surgery and continued for 24 hours postoperatively as a drip at 1 mg kg^{-1} h^{-1}. Platelet levels are maintained greater than 100,000 mm^3, fibrinogen levels are greater than 1 g/l and activated clotting times levels are decreased by 20% (reference values, 200-230 seconds) for 24 hours. Clotting status is evaluated after the procedure by measuring platelets, hemoglobin level, fibrinogen level, activated partial thromboplastin time, and factor V Leiden, and levels are corrected if necessary. If the fibrinogen level is lower than 1 g/l, fibrinogen (Haemocomplettan; CSL Behring, Breda, the Netherlands) is given in doses of 0.5 to 1 g as a drip for 30 minutes.

1.4. Variables

The following demographic data were collected for all patients treated in our institution: sex, gestational age in weeks, birth weight in kilograms, Apgar score at 1 minute, side of the diaphragmatic defect (left/right), type of CDH repair (primary or patch), ECMO mode (venous-arterial or venovenous), and age at repair in days.

The group of patients undergoing CDH repair on ECMO was compared with the group undergoing repair after cessation of ECMO. The primary outcome measure was the occurrence of surgery-related bleeding complications. Surgical site bleeding was scored positive if extra-fluid expansion, transfusion, or relaparotomy caused by postoperative bleeding was reported in the charts and data derived from our data management system (patient data management system, or PDMS). This is a computer-based prospective collection of all physiologic parameters

including the amount of fluid, ventilation settings, and, eventually, ECMO settings. Because of the change in timing of CDH repair over time in our institution, analysis was performed in 3 subgroups, indicative of 3 different periods, to try to eliminate other confounding treatment factors that might influence the primary outcome. The entire patient population with CDH was, thus, subdivided into 3 groups to indicate the number of patients operated on or off ECMO. During the study period, the entry criteria for ECMO in CDH did not change.

Secondary outcome measures were length of stay in ICU in days, duration of mechanical ventilation in days, ECMO runtime in days, and duration of CDH repair in minutes.

1.5. Comparison with the ELSO registry

Data derived from the ELSO registry were used to correlate our data to a large international patient cohort. All patients with CDH undergoing repair in this registry from 1984 until 2008 who had ECMO treatment were included, and surgery-related bleeding complications were compared with those findings in our institution. Surgical site bleeding was scored positive according to the supplied data from the ELSO registry database.

1.6. Statistics

Three investigators collected data from patient charts and existing databases in an Excel spreadsheet (Microsoft Excel Redmond, WA 98052, USA). Subsequently, all data were exported to SPSS for statistical analysis (SPSS, Chicago, IL). Normally distributed continuous variables were compared using the Student t test, whereas nonnormally distributed variables were analyzed using the Mann-Whitney U nonparametric test. To compare categorical variables, χ^2 and Fisher exact tests were performed. A P value less than .05 was considered statistically significant.

The institutional review board of Erasmus MC–Sophia, Rotterdam, the Netherlands, approved the study.

2. Results

2.1. Results from Erasmus MC–Sophia

Between January 1995 and May 2008, 195 patients with CDH were admitted to our institution. Of this group, 129 (66.2%) underwent repair of the diaphragmatic defect. Initially, survival was 50% and has increased over the years to 85% during the last 3 years [10]. Of all the patients undergoing CDH repair, 51 (39.5%) required ECMO treatment. Three patients underwent CDH repair and required ECMO treatment afterward; these patients were excluded from this study. All patients underwent venous-arterial ECMO. Demographic data are summarized in Table 1. Sex, mean gestational age at birth, mean birth weight, side of the hernia, and median APGAR score after 1 minute were not significantly different.

Table 1 Demographic data from Erasmus MC–Sophia

	Repair on ECMO	Repair off ECMO	P
n	32	16	
Birth weight (kg), mean ± SD	3.04 ± 0.65	3.21 ± 0.43	.714 [a]
Gestational age (wk), mean ± SD	38.63 ± 1.76	39.0 ± 1.15	.121 [a]
Sex (M/F), no.	21/11	8/8	.297 [b]
Side hernia (left/right)	15/1	29/3	.348 [b]
Median Apgar score at 1 min (IQR)	5 (2)	7 (4)	.124 [c]

M indicates male; F, female.
[a] t Test.
[b] χ^2 test.
[c] Mann-Whitney U nonparametric test.

In our institution, surgery-related bleeding complications after CDH repair on ECMO (4/32 patients, or 12.5%) were higher but not significantly different from surgery-related bleeding complications after repair off ECMO (1/16 patients, or 6.25%) (P = .652; see Table 2). Changes in management over time could result in potential bias, and therefore, a subgroup analysis was performed for 3 different periods: 1995 to 1999, 2000 to 2004, and 2005 to 2008. Since 2005, CDH repair in patients requiring ECMO was only performed on ECMO (Fig. 1). In contrast, during the first study period when ECMO was instituted (1995-1999), half of the patients had CDH repair off ECMO.

2.2. Results of surgical site bleeding from the ELSO registry

The group of patients undergoing CDH repair on ECMO was larger than that off ECMO in the ELSO registry during all periods (Fig. 2). The ELSO registry registered surgical site bleeding in its database for all patients that had repair of their CDH. Table 2B demonstrates that between 1984 and

Table 2 Bleeding complications: Erasmus MC–Sophia vs ELSO registry

	Surgery-related bleeding complications		Total
	Yes	No	
(A) Erasmus MC–Sophia			
On ECMO	4	28	32
Off ECMO	1	15	16
(B) ELSO registry			
On ECMO	616	1614	2230
Off ECMO	34	1075	1109

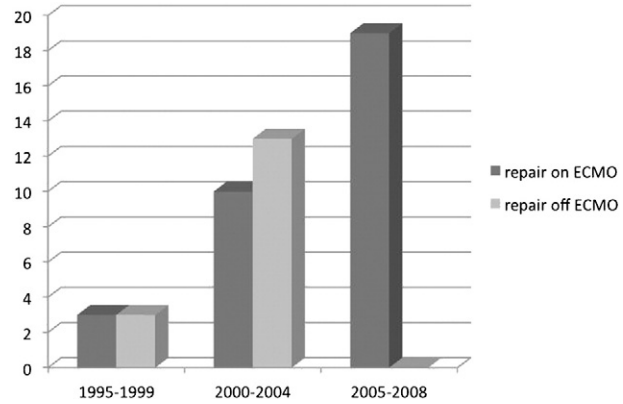

Fig. 1 The number of patients operated on or off ECMO during 3 different periods. After 2005, all patients were operated on ECMO.

2008, in the ELSO registry, 616 (27.6%) of 2230 patients undergoing CDH repair on ECMO were reported to have surgical site bleeding compared with 34 (3.07%) of 1109 patients undergoing CDH repair off ECMO ($P < .0001$).

2.3. Secondary outcome measures of Erasmus MC–Sophia

2.3.1. Surgical data

Surgical data are summarized in Table 3. The number of patients undergoing CDH repair using a patch was 42 (87.5%) and was not significantly different in both groups. In the repair on ECMO group, 6.6% (2/30) had a primary repair compared with 12.5% (2/16) in the off-ECMO repair group ($P = .602$). For 2 patients, it was not known whether the repair was done by using a patch or by primary closure of the diaphragmatic defect. Operating time between the 2 groups was also not different. The median operating time was 2.0 hours in the on-ECMO repair group compared with 1.9 hours in the off-ECMO repair group ($P = .188$). Patients undergoing CDH repair on ECMO were significantly younger compared with those repaired off ECMO. The median age at repair in the on-ECMO repair group was 5.0 days (interquartile range [IQR], 5 days) compared with 20.5 days (IQR, 23 days) in the off-ECMO repair group ($P < .0001$).

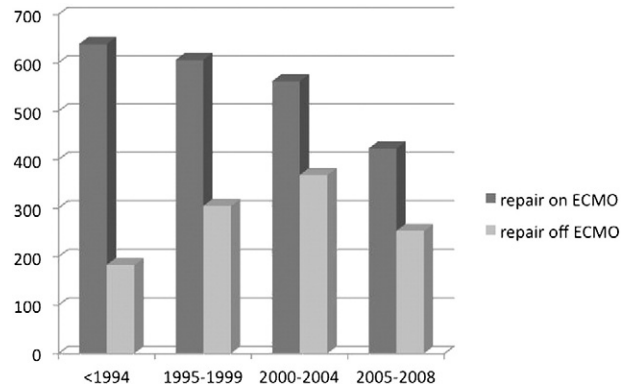

Fig. 2 The number of patients operated on or off ECMO during 4 different periods, as registered in the ELSO registry database.

Table 3 Surgical data

	Repair on ECMO	Repair off ECMO	*P*
Primary/patch closure [a]	2/28	2/14	.602 [b]
Time of repair (h), median (IQR)	2.00 (0.65)	1.9 (1.07)	.188 [c]
Age at repair (d), median (IQR)	5.0 (5.0)	20.5 (22.50)	.000 [c]

[a] Missing values: for 2 patients, information on whether a patch was used for the repair could not be retrieved.
[b] χ^2 Test.
[c] Mann-Whitney *U* nonparametric test.

2.3.2. Extracorporeal membrane oxygenation/ventilation data

There was no difference in days of admission to the ICU and duration of mechanical ventilation between the 2 groups (Table 4). Patients undergoing repair on ECMO had a median ICU stay of 37 days (IQR, 59 days) compared with 57 days (IQR, 62 days) in the group that had repair after ECMO ($P = .404$). The median number of days requiring mechanical ventilation was 21 days (IQR, 28 days) in patients undergoing repair on ECMO compared with 28 days (IQR, 34 days) in those undergoing repair off ECMO. However, ECMO runtime was significantly less in the off-ECMO repair group. Median ECMO runtime in the group that had repair on ECMO was 9.77 days (IQR, 8 days) compared with 7.11 days (IQR, 5 days) in the off-ECMO group ($P = .041$).

3. Discussion

To our knowledge, this is the first study to demonstrate the feasibility of neonatal CDH repair on ECMO using a specific anticoagulant protocol. Although we found a higher bleeding complication rate in the group repaired on ECMO, this percentage was not statistically significant and lower than the

Table 4 ECMO/ventilation data

	Repair on ECMO	Repair off ECMO	*P*
ECMO runtime (d), median (IQR)	9.77 (8)	7.11 (5)	.041 [a]
Time on mechanical ventilator (d), median (IQR)	21 (28)	27.67 (33.63)	.552 [a]
Time on ICU (d), median (IQR)	37 (59.23)	57 (62)	.404 [a]

[a] Mann-Whitney *U* nonparametric test.

number reported in the ELSO registry. This is despite the fact that the definition of surgery-related bleeding complications was less well defined in the ELSO registry as compared with our group. This corroborates previous reports that observed more surgery-related bleeding complications when repair was done on ECMO [11-13]. In addition, we observed a trend toward a shorter length of stay in the ICU in the on-ECMO repair group as well as a trend toward a shorter duration of mechanical ventilation in the on-ECMO repair group compared with the off-ECMO repair group. However, changes in management over time have certainly contributed [10,14].

Results from the ELSO registry indicate that currently more patients with CDH treated with ECMO are operated on ECMO than off ECMO internationally. In 1997, van der Staak et al [11] reported that repair on ECMO may increase the risk of bleeding complications and that these complications can be a hallmark of poor outcome. The administration of TEA is effective in reducing hemorrhagic complications but might increase the risk of thrombotic complications. However, after introducing our specific perioperative bleeding prevention protocol, we did not observe more clotting problems in the ECMO circuit and/or oxygenator. Since the establishment of a protocol to prevent complications from bleeding in 2003, we used TEA during all our repairs on ECMO, and data from the ELSO registry database did not indicate the use of TEA. In addition to the importance of antifibrinolytic agents in a specific perioperative bleeding prevention protocol like ours, the importance of delicate and meticulous surgical technique should not be underestimated.

Vazquez and Cheu [12] report that surgery-related site bleeding complications, as well as overall hemorrhagic complications, were significantly higher in patients undergoing CDH repair on ECMO. These data also included the data from the ELSO registry and were derived from 88 ECMO centers during the period of January 1989 until December 1991. In addition, they reported that patients repaired on ECMO are more prone to have acidosis and hypoxia compared with those that had repair off ECMO. However, both acidosis and hypoxia were associated with hemorrhage, and the authors did not report significant differences in these parameters between both groups. Another retrospective study performed by Sigalet et al [13] in 1995 demonstrated that in a group of 60 patients with CDH, the 9 patients who had repair on ECMO required a significantly higher transfusion volume and advised against repair of CDH on ECMO.

One of the limitations of our study is the small number of patients (N = 48). The low observed frequencies of bleeding complications in both groups of our series make it difficult to draw firm conclusions about significant differences. However, a more relevant finding from our study is that we observed only 12.5% bleeding complications in the group repaired on ECMO, despite the fact that we used a broader definition of bleeding complications than did the ELSO registry.

Another limitation is the retrospective character of our study. At Erasmus MC–Sophia, surgery-related bleeding complications were scored positive if extra-fluid expansion, transfusion, or relaparotomy caused by postoperative bleeding was specifically reported in our prospective computerized PDMS. Although before 2003, information was retrieved from patient charts, our data were very reliable from that time point onward because patients were operated on in the ICU, and therefore, all data including extra fluids are integrated prospectively in PDMS.

The data from the ELSO registry was lacking demographic data and potentially very different among centers. Moreover, the ECMO and anticoagulant protocol used in ELSO patients was not reported. Differences in anticoagulant protocols could, therefore, result in substantial bias in this analysis because this was found to be a major determinant of hemorrhagic complications in our series at Erasmus MC–Sophia. Surgery-related site bleeding complications reported in the ELSO registry were not well defined, and data in this registry originate from different hospitals; hence, correcting for these data is not possible. Because we used a broader definition of surgery-related site bleeding complications, our bleeding complications are probably overestimated as compared with the norm of the ELSO registry. Our bleeding complications in the on-ECMO repair group were lower than reported in the ELSO registry: 12.5% vs 27.6%. We chose not to compare our numbers statistically to the numbers of the ELSO registry because of a lack of a clear definition of surgery-related bleeding complications in the latter group.

Days in the ICU and duration of mechanical ventilation were reviewed as secondary outcome measures in our series. We observed a trend toward a shorter ICU stay and a shorter period of mechanical ventilation in the patients repaired while on ECMO. This trend was not statistically significant and is probably more related to modern ICU management than to the actual repair on ECMO. Because of the small sample size, matching of patients was not possible. These parameters were not measured in the population from the ELSO registry.

Although this is a retrospective study that has its limitations as stated previously, in our single center with 13-year experience period, no major surgery-related bleeding complications were observed in our institution while performing repair of CDH on ECMO. In addition, we noted a trend toward a shorter ICU stay and a shorter period of requiring mechanical ventilation. In the past 5 years, all patients with CDH requiring ECMO were repaired while on ECMO in our institute, without major bleeding complications.

Congenital diaphragmatic hernia repair on ECMO is feasible, and using a specific anticoagulation protocol with TEA resulted in a low complication rate. A larger prospective study should be performed to evaluate whether there are indeed differences in surgery-related bleeding complications and which coagulant protocol should be used to perform CDH repair on ECMO as safely as possible.

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