Journal of Pediatric Surgery 59 (2024) 161766

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

Optimizing Congenital Diaphragmatic Hernia Repair on ECMO: Evaluating the Risk of Bleeding

Nicholas Schmoke [a], Anna Rose [a, b], Christopher Nemeh [a], Yeu Sanz Wu [a], Pengchen Wang [c], Paul Kurlansky [c, d], Cindy Neunert [e], William Middlesworth [a], Vincent Duron [a, *]

[a] Division of Pediatric Surgery, Department of Surgery, Columbia University Vagelos College of Physicians and Surgeons/NewYork-Presbyterian Morgan Stanley Children's Hospital, New York, NY, USA
[b] Columbia University Vagelos College of Physicians & Surgeons, New York, NY, USA
[c] Center for Innovation and Outcomes Research, Department of Surgery, Columbia University Irving Medical Center, New York, NY, USA
[d] Division of Cardiac, Thoracic, and Vascular Surgery, Department of Surgery, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA
[e] Division of Pediatric Hematology, Oncology, and Stem Cell Transplant, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons/NewYork-Presbyterian Morgan Stanley Children's Hospital, New York, NY, USA

ARTICLE INFO

Article history:
Received 20 March 2024
Received in revised form
28 July 2024
Accepted 19 August 2024

Keywords:
Congenital diaphragmatic hernia
Extracorporeal membrane oxygenation
Bleeding

ABSTRACT

Background: Institutions lack consensus on the management of patients with congenital diaphragmatic hernia (CDH) who are repaired on extracorporeal membrane oxygenation (ECMO). Our study aimed to evaluate risk factors associated with bleeding complications in patients with CDH repaired on ECMO.
Methods: A single-institution retrospective review evaluated all patients with CDH who underwent on-ECMO repair between January 2005 and December 2023. A significant bleeding complication post-repair was defined as bleeding necessitating re-operation. The association between preoperative factors and bleeding complications was evaluated.
Results: Forty-six patients were included. Bleeding complications developed in 11/46 (24%) patients. Birthweight (2.5 vs. 3.2 kg, $p = 0.02$), platelet count <100/mm^3 (64% vs. 29%, $p = 0.04$), elevated blood urea nitrogen (BUN; 24.5 vs. 17.5 mg/dL, $p = 0.05$), and older age at repair (8 vs. 5 days, $p = 0.04$) were associated with bleeding. In univariate analysis, patients with platelets under 100/mm^3 were more likely to develop a bleeding complication (OR = 4.4, $p = 0.04$). Patients who experienced a significant bleeding event experienced increased ECMO days (12 vs. 7 days, $p < 0.01$), ventilator days (31 vs. 18 days, $p < 0.05$), and lower survival to discharge (36% vs. 74%, $p = 0.03$).
Conclusion: Among CDH patients undergoing repair on ECMO, those with lower birth weight, platelet counts under 100/mm^3, elevated BUN, and older age at repair had an increased risk of a significant bleeding complication, resulting in more ECMO and ventilator days and higher mortality. Patients undergoing on-ECMO repair should have platelet count transfused to greater than 100/mm^3. Patients at high risk for bleeding may benefit from early repair on ECMO.
Level of Evidence: Level III.

1. Introduction

Neonates with congenital diaphragmatic hernias (CDH) can present with a wide range of disease severity, ranging from asymptomatic to critically ill. Patients with refractory respiratory failure or hemodynamic instability frequently require advanced life support with extracorporeal membrane oxygenation (ECMO). In critically ill neonates requiring ECMO, there remains a lack of consensus on the optimal timing of CDH repair. Advocates of repair

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; BUN, blood urea nitrogen; aPTT, activated partial thromboplastin time; INR, international normalization ratio; IQR, interquartile range; MIS, minimally invasive surgery; TEG, thromboelastography; ROTEM, rotational thromboelastometry; LHR, lung-to-head circumference ratio; ACT, activated clotting time.

* Corresponding author. Division of Pediatric Surgery, Morgan Stanley Children's Hospital, 3959 Broadway, CHN 215, New York, NY 10032, USA.
E-mail address: Vd2312@cumc.columbia.edu (V. Duron).

https://doi.org/10.1016/j.jpedsurg.2024.161766
0022-3468/

following ECMO decannulation report the increased risk of bleeding complications and associated morbidity with on-ECMO repair [1–4]. Alternatively, repair on ECMO provides cardiorespiratory support for recovery after physiologic insult of surgery. Proponents of early repair on ECMO report optimized outcomes due to earlier improvement in pulmonary physiology combined with minimized ECMO-related complications [3,5–7].

Maintaining adequate anticoagulation while minimizing patient and circuit thrombosis is a delicate balance for all pediatric patients on ECMO. In single-institution reviews, central cannulations, older age at repair, elevated blood urea nitrogen (BUN), low platelet counts, and high lactate have been associated with increased bleeding events [7,8]. Multiple interventions to minimize bleeding in pediatric patients on ECMO have been explored, including advanced coagulation monitoring with whole blood viscoelastic testing, correction of coagulopathy with variable transfusion thresholds, and the targeted administration of antifibrinolytic agents [9–13].

Despite these advancements, it remains unclear how to further mitigate the risk of bleeding in patients with CDH undergoing repair on ECMO. Our study aimed to evaluate factors associated with bleeding complications in patients with CDH undergoing repair on ECMO. We hypothesized that patients with increased markers of coagulopathy at the time of CDH repair would have increased bleeding complications.

2. Methods

2.1. Study design and setting

A single-institution retrospective review at a quaternary care academic children's hospital was completed between January 2005 and December 2023. The Columbia University Institutional Review Board approved the study, approval number AAAR0525. Inclusion criteria were patients with CDH requiring ECMO who underwent on-ECMO CDH repair.

2.2. Data collection

Baseline demographics, including gender, birthweight, gestational age, CDH laterality, type of repair, and surgical approach, were extracted from electronic medical records. Risk factors for postoperative bleeding were assessed, including age at repair, days on ECMO pre-repair, age of ECMO circuit on the day of repair, preoperative coagulation profiles, BUN level, preoperative administration of antithrombin III or an antifibrinolytic agent, and intraoperative administration of hemostatic agents, including SURGICEL Hemostat (Ethicon Inc., NJ, USA), TachoSil Fibrin Sealant Patch (Corza Medical, MA, USA), and FLOSEAL Hemostatic Matrix (Baxter, IL, USA). Coagulation profiles included activated partial thromboplastin time (PTT), international normalization ratio (INR), platelet counts, hemoglobin, and hematocrit. All laboratory values were reported as the average of the two most recent preoperative values to mitigate variation in laboratory results.

2.3. Outcomes

The primary outcome was significant bleeding complication, defined as bleeding necessitating re-operation. Secondary outcomes were total days on ECMO, total days on ventilator, length of stay, survival to discharge, and disposition at discharge.

2.4. Anticoagulation management

Per institutional protocol, all pediatric patients on ECMO received unfractionated heparin for systemic anticoagulation. From 2005 through 2012, patients were monitored with activated clotting time (ACT) levels with a goal of 180–220 s. In 2013, anticoagulation monitoring transitioned to anti-factor Xa levels with a goal of 0.3–0.7 IU/mL. Additionally, all patients on ECMO had a routine antithrombin III level sent daily beginning in 2012, with antithrombin replacement occurring in those who remained subtherapeutic on heparin infusions greater than 40 units/kg/hr. Furthermore, patients undergoing CDH repair on ECMO received aminocaproic acid (AMICAR) 2 h prior to repair, with an infusion continued for 48 h postoperatively unless otherwise contraindicated.

2.5. Operative approach

All patients underwent an open CDH repair via a subcostal incision. Small defects were closed primarily, while large defects had a synthetic patch placed. An intrabdominal drain was left in place in all patients at the time of repair.

2.6. Statistical analysis

R programming language (4.3.1, R Foundation) was used for all analyses and table generation. The normality of the distribution of continuous data was assessed using the Shapiro–Wilk test. A predetermined alpha level of $\leq$0.05 was used to determine statistical significance. Categorical variables are reported as count and frequency and compared using the Chi-Square or Fisher's Exact test as appropriate. Continuous variables are reported as a median and interquartile range due to their non-normality and compared using the Mann–Whitney U test. Univariate linear and logistic models further evaluated the association between preoperative risk factors and bleeding complications.

3. Results

In total, 294 neonates were treated for CDH, of which 53 out of 294 (18%) required ECMO. Three patients died before they underwent repair, and four patients were decannulated prior to repair. Forty-six patients who underwent CDH repair on ECMO were included in the study. Patient demographics are presented in Table 1. The median birthweight was 3.0 kg (IQR 2.5–3.5), and the median gestational age was 38.0 weeks (IQR 37.0–39.1). There were 33 (72%) male patients, and 32 (70%) had a left-sided CDH. 22 (48%) patients had an isolated CDH, and the median prenatal lung-to-head circumference ratio (LHR) was 1.0 (IQR 0.9–1.2). All patients were cannulated onto veno-arterial ECMO. All patients underwent an open surgical approach; 43 (93%) had a patch repair, while 3 (7%) had a primary repair. No patients had culture-positive sepsis or were on dialysis at the time of CDH repair. Apgar scores were assessed at 5 min.

Primary and secondary outcomes are presented in Table 2. A significant bleeding complication necessitating re-operation developed in 11/46 patients (24%). The median number of days prior to takeback was 1.0 days (IQR 0.5–2.0). Indications for return to the operating room were repeated transfusion requirements in seven patients and abdominal compartment syndrome in five patients. Four patients required more than one takeback. The median time on ECMO and a ventilator were 7.0 days (IQR 5.3–10.0, range 1.0–21.0) and 19.5 days (IQR 13.3–27.0), respectively. Thirty-four patients (65%) survived to discharge with a median length of stay of 56.0 days (IQR 29.8–92.3). Forty-three patients (93%) had neuroimaging completed prior to discharge.

Lower median birthweight (2.5 vs. 3.2 kg, $p = 0.02$), platelet counts less than 100/mm^3 (64% vs. 29%, $p = 0.04$), older age at repair (8 vs. 5 days, $p = 0.04$), and elevated BUN (24.5 vs. 17.5 mg/dL, $p = 0.05$) were associated with a significant bleeding complication

Table 1
Patient demographics (n = 46).

Gender	
- Male	72% (33)
- Female	28% (13)
Birthweight	3.0 kg [2.5–3.5]
Gestational age	38.0 weeks [37.0–39.1]
Diagnosed prenatally	93% (43)
Prenatal LHR	1.0 [0.9–1.2]
Isolated CDH	48% (22)
CDH location	
- Left	70% (32)
- Right	30% (14)
Postnatal factors (pre-ECMO)	
- Apgar score	7 [5–8]
- Low pH	7.04 [6.91–7.13]
- High pH	7.38 [7.33–7.43]
- Low pCO2	37 [30–36]
- High pCO2	94 [80–119]
Type of repair	
- Primary	7% (3)
- Patch	93% (43)
Surgical approach	
- Open	100% (46)
- MIS	0% (0)

CDH = Congenital diaphragmatic hernia, MIS = Minimally invasive surgery, LHR = Lung-to-head circumference ratio, pCO2 = partial pressure carbon dioxide.

Table 2
Outcomes following CDH repair on ECMO.

Days on ECMO	7.0 days [5.3–10.0]
Days on ventilator	19.5 days [13.3–27.0]
Bleeding necessitating re-operation	24% (11)
Length of stay	56.0 days [29.8–92.3]
Survival to discharge	65% (30)
Discharge location	
- Home	41% (19)
- Transferred	15% (7)
- Subacute rehab	9% (4)
- Deceased	35% (16)

CDH = Congenital diaphragmatic hernia, ECMO = Extracorporeal membrane oxygenation.

(Table 3). In a univariate logistic model, the odds of patients with platelet counts less than 100/mm^3 developing a bleeding complication were 4.4 times the odds of those with platelet counts more than or equal to 100/mm^3 ($p = 0.04$). Additionally, the odds of developing a bleeding complication increased by 41% for each additional day of age prior to repair ($p = 0.03$).

In a secondary analysis evaluating the effect of postoperative bleeding on patient outcomes (Table 4), a significant bleeding complication was associated with increased ECMO days (12 vs. 7 days, $p < 0.01$), increased ventilator days (31 vs. 18 days, $p = 0.05$) and lower survival to discharge (36% vs. 74%, $p = 0.03$). While there was a trend for increased incidence of intracranial hemorrhage (ICH) in patients with a bleeding complication, statistical significance was not reached (30% vs 6%, $p = 0.07$). In a univariate linear regression model, a significant bleeding complication resulted in an additional 2.9 ECMO days ($p = 0.02$), an additional 29.2 ventilator days ($p = 0.01$), and 80% lower odds of survival ($p = 0.03$).

4. Discussion

Critically ill neonates with CDH undergoing repair on ECMO are at risk for significant bleeding complications. The results of the present study demonstrate that among neonates undergoing repair on ECMO, those with lower birth weight, platelet counts under 100/mm^3, elevated BUN, and older age at repair had an increased risk of a significant bleeding complication resulting in more ventilator and ECMO days and higher mortality. These results suggest that patients repaired on ECMO should have platelets transfused and maintained to greater than 100/mm^3 and that bleeding risks may be mitigated by pursuing early repair on ECMO. These findings can help clinicians minimize bleeding complications for at-risk patients and guide decision-making regarding the risks and benefits of on vs. off-ECMO repair.

Our results of increased bleeding risk in patients with elevated BUN and older age at the time of repair are consistent with other reports in the literature. In a 2023 review of 146 infants who underwent on-ECMO CDH repair, the bleeding risk was increased in those who underwent repair more than 48 h after cannulation (36% vs. 5%, $p < 0.01$), with those who underwent delayed repair having a greater than 11 times odds of developing a bleeding complication [7]. Additionally, the authors found that patients with a bleeding complication had a significantly elevated BUN compared to those without a bleeding complication (63 vs. 9 mg/dL, $p < 0.01$) [7].

In a review of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) results in pediatric patients on ECMO, platelet dysfunction was the most common abnormality identified and is likely a complex multifactorial process [11]. In addition, a recent prospective study found evidence of acquired von Willebrand disease in 100% of pediatric patients on ECMO, further contributing to an increased risk of bleeding [14]. Platelet transfusion thresholds for neonatal and pediatric ECMO continue to vary widely, with a survey of medical directors reporting ranges from 50/mm^3 to 100/mm^3, and there is an ongoing NIH trial comparing liberal and restrictive platelet transfusion strategies [9,15]. Our results suggest that patients repaired on ECMO would benefit from having their platelet count transfused to greater than 100/mm^3 prior to repair.

Maintaining adequate anticoagulation while minimizing patient and circuit thrombosis remains a delicate balance. Per institutional protocols, all patients in our series received heparin as their primary anticoagulant while on ECMO. Emerging evidence on direct thrombin inhibitors as an alternative to heparin is promising. In a 2022 systematic review and meta-analysis comparing the efficacy and safety of bivalirudin to heparin, bivalirudin demonstrated a reduced incidence of major bleeding in children, patient thrombosis, in-circuit thrombosis, and in-hospital mortality [16]. Additionally, aminocaproic acid has been shown to reduce bleeding and blood product requirements in pediatric cardiac patients on ECMO [12]. Interestingly, we found no difference in bleeding complications in patients who received an aminocaproic acid infusion 2 h prior to CDH repair compared to those who did not. This may highlight the intricate differences between intraoperative ECMO and cardiopulmonary bypass circuits [17].

Limitations of our study include those inherent to a single-center retrospective review and a small sample size. Multiple variables, including anti-factor Xa, antithrombin III, plasma-free hemoglobin, and CDH defect size, were not collected early in our study period, which prevented a meaningful comparison. Additionally, TEG and ROTEM are not readily available at our institution and, therefore, excluded from this study. The small sample size limited the ability to perform multivariable analyses to identify factors independently associated with outcomes of interest more clearly. Finally, all patients in our study underwent an open operative approach, and 93% received a patch repair; other institutions have reported their experience with additional approaches and repair methods, including a muscle-flap technique, which likely results in variable bleeding risks and may limit generalizability [18].

Our average number of days on ECMO at the time of repair was four days for both groups. Over the course of the study, we have progressed towards early repair on ECMO (within 48 h of

Table 3
Evaluation of risk factors associated with postoperative bleeding.

	No Bleeding Complication (n = 35)	Bleeding Complication (n = 11)	p-value
Birthweight	3.2 kg [2.6–3.5]	2.5 kg [2.4–3.0]	**0.02**
Gestational age	38.0 weeks [37.0–39.2]	37.7 weeks [36.0–38.6]	0.17
CDH location			0.46
- Left	66% (23)	82% (9)	
- Right	34% (12)	18% (2)	
Type of repair			>0.99
- Primary	9% (3)	0% (0)	
- Patch	91% (32)	100% (11)	
Age at repair	5.0 days [4.0–6.5]	8.0 days [5.5–9.5]	**0.04**
Days on ECMO pre-repair	4.0 days [3.0–5.0]	4.0 days [3.5–7.0]	0.26
Age of circuit on day of repair	4.0 days [3.0–5.0]	4.0 days [2.5–6.0]	0.98
Pre-op aPTT (seconds)	114.6 [84.7–180.0]	129.1 [92.0–159.7]	0.81
Pre-op INR			>0.99
- ≤1.4	69% (24)	64% (7)	
- >1.4	31% (11)	36% (4)	
Pre-op platelet count			**0.04**
- <100 mm^3	29% (10)	64% (7)	
- ≥100 mm^3	71% (25)	36% (4)	
Pre-op hemoglobin	14.1 g/dL [13.1–14.6]	13.1 g/dL [12.5–14.6]	0.42
Pre-op hematocrit	40.6% [37.8–42.1]	38.7% [36.0–41.3]	0.13
Pre-op white blood cell count	7.6 mm^3 [6.8–8.9]	8.9 mm^3 [6.8–11.6]	
Pre-op BUN	17.5 mg/dL [13.8–25.8]	24.5 mg/dL [21.3–32.3]	**0.05**
Antithrombin III administered pre-op	6% (2)	18% (2)	0.24
Antifibrinolytic agent administered pre-op	71% (24)	64% (7)	0.72
Intra-op hemostatic agents	20% (7)	27% (3)	0.68

CDH = Congenital diaphragmatic hernia, ECMO = Extracorporeal membrane oxygenation, aPTT = Activated partial thromboplastin time, IQR = Interquartile range, INR = International normalization ratio, BUN = Blood urea nitrogen.

Table 4
Effect of postoperative bleeding on patient outcomes.

	No Bleeding Complication (n = 35)	Bleeding Complication (n = 11)	p-value
Days on ECMO	7.0 days [5.0–9.5]	12.0 [8.0–14.0]	**<0.01**
Days on ventilator	18.0 days [12.0–23.5]	31.0 [17.0–38.5]	**0.05**
ICH prior to discharge	6% (2)	30% (3)	0.07
Length of stay	54.0 days [32.5–80.0]	58.0 days [18.0–97.0]	0.74
Survival to discharge	74% (26)	36% (4)	**0.03**
Disposition at discharge			**0.04**
- Home	51% (18)	9% (1)	
- Transferred	14% (5)	18% (2)	
- Subacute rehab	9% (3)	9% (1)	
- Deceased	26% (9)	64% (7)	

ECMO = Extracorporeal membrane oxygenation, ICH = Intracranial hemorrhage.

cannulation) for patients we believe will be on a prolonged ECMO run to prevent the complications associated with late repair on ECMO and to reduce the likelihood of non-repair, and repair after ECMO for patients we anticipate will have a short run on ECMO [4–6,19,20]. The present study's findings have informed our practice to transfuse platelet counts to greater than 100/mm^3 for patients we repair on ECMO and work towards early repair on ECMO for those at increased bleeding risk, including those with low birth weight and elevated BUN. Additionally, our institution's total median days on ECMO for patients with CDH are lower than reports elsewhere in the literature [1,21,22]. While numerous factors contribute to the ability to successfully liberate a neonate from ECMO, our institution has a long history of multidisciplinary CDH management originating with Drs. Jen-Tien Wung (neonatology) and Charles Stolar (pediatric surgery), highlighting the importance of a collaborative approach.

5. Conclusion

The risks and benefits of CDH repair on- vs. off-ECMO require careful consideration. Neonates with lower birth weights, platelet counts under 100/mm^3, elevated BUN, and older age at the time of CDH repair on ECMO have an increased risk of a significant bleeding complication. Bleeding complications consequently were related to longer duration of ECMO and ventilator support as well as increased in-hospital mortality. Neonates undergoing on-ECMO repair should have platelet counts transfused to greater than 100/mm^3. Patients at increased risk for a significant bleeding complication, including those with low birth weight and elevated BUN, may benefit from early repair on ECMO to reduce the risk of bleeding. Future studies to further evaluate how to mitigate bleeding risks on ECMO will be beneficial for improving the management of these complex neonates with CDH.

Previous Communication

The abstract was presented at the 40th Annual Children's National Symposium: ECMO and the Advanced Therapies for Cardiovascular and Respiratory Failure in Keystone, CO, on February 27th, 2024.

Financial Support statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

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