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Improved mortality rate for congenital diaphragmatic hernia in the modern era of management: 15 year experience in a single institution

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Abstract

Background/Purpose—Mortality rates with congenital diaphragmatic hernia (CDH) have remained at approximately 30% for the last 2 decades. Therapies targeting pulmonary hypertension (PHTN) have not been systematically studied in this population, but are increasingly used. We hypothesized that incremental changes in treatments for PHTN have improved mortality for CDH infants.

Methods—Prospective data from 1998–2013 on all liveborn CDH patients treated at our institution were retrospectively analyzed. Based on management of PHTN, 4 Eras were identified for comparison. Logistic and linear regression were used to compare characteristics. The primary outcome of death prior to discharge was analyzed by multivariable Cox regression modeling.

Results—The study included 192 infants who met inclusion criteria. Length of stay increased, while rates of primary repair decreased, suggesting a sicker cohort in the most recent Eras. Analysis of mortality across 4 Era's showed no difference. By post-hoc analysis, ECMO availability was associated with mortality reduction for Era's 3–4 versus 1–2 (HR=0.27, $p < 0.001$).

Conclusions—Improved survival at our institution may be related to recent introduction of ECMO and more aggressive approaches to pulmonary hypertension. Further systematic studies of these PHTN therapies in this specific population are warranted.

Keywords

Congenital diaphragmatic hernia; Pulmonary hypertension; Mortality; ECMO

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Congenital diaphragmatic hernia (CDH) occurs in approximately 1:2000 to 1:5000 live births. [1, 2] Despite advances in medical and surgical treatment, overall survival has remained at approximately 70% over the past 2 decades. [3, 4] Pulmonary hypoplasia and persistent pulmonary hypertension (PHTN), a primary target of treatment, are the main predictors of prognosis in patients with isolated CDH.

Despite conflicting results for a survival benefit, pre-operative extracorporeal membrane oxygenation (ECMO) has increased over the past 2 decades in CDH patients. [5,6] The NINOS trial demonstrated inhaled nitric oxide (iNO) improved oxygenation and reduced the need for ECMO in late-preterm/term infants with PHTN; however, this was not borne out in the subset of CDH patients. [7, 8] Despite this evidence, currently approximately 60% of CDH patients reported to the CDH Study Group Registry receive iNO. [Personal communication, Dr. Kevin Lally]

Over the past decade other pulmonary vasodilators have been introduced in the management of CDH-associated PHTN, including intravenous prostacyclin and milrinone. Prostacyclin, also known as prostaglandin I_2 (PGI_2), promotes vascular smooth muscle relaxation. Milrinone, a phosphodiesterase-3 inhibitor, has several actions including direct pulmonary vasodilation, inotropic improvement in systolic function, and a lusitropic effect to improve diastolic function. [9] The use of PGI_2 and/or milrinone in the treatment of CDH-associated PHTN has not been systematically studied. [9, 10]

Despite limited supporting evidence, we have noted increasing use of iNO since 2000, the introduction of ECMO in 2003, and more common use of PGI_2 and milrinone beginning in 2005, at our institution. It is unclear if mortality has significantly improved since incorporating these treatment options into our approach to CDH management. We hypothesized that there would be a time dependent effect on survival related to the introduction of iNO, ECMO, and IV pulmonary vasodilators (PGI_2 /milrinone) for infants with CDH managed at the University of Utah and Primary Children's Hospital over the past 15 years.

METHODS

Study Population

After approval by the University of Utah Institutional Review Board, all liveborn infants with CDH from January 1998 to June 2013 were identified from our CDH database, prospectively maintained as a participating institution in the CDH Study Group registry. We retrospectively analyzed the database to obtain demographic, preoperative, operative, and disposition information. Patients were excluded if they had a delayed diagnosis after 24 hours of life, chromosomal disorders or severe congenital anomalies with poor prognosis, initial management and operative repair at another hospital, if unable to be stabilized or ventilated in first few hours of life, or if parents declined treatment.

Patient Management Strategy

Written guidelines for the management of patients with CDH in our neonatal intensive care unit (NICU) were developed in 2007 and include a strategy of gentle ventilation, treatment

aimed to minimize pulmonary hypertension, and a non-emergent approach to operative repair. Gentle ventilation is accomplished using high-frequency oscillatory ventilation. Moderate hypercarbia is tolerated and mean airway pressures are typically initiated at 11–12 cm H_2O, with maximum mean airway pressure limits of ≤16 cm H_2O. Recommended pre-ductal oxygen saturation limits are > 90%. Per protocol, infants who fail to reach a pre-ductal oxygen saturation of 85% or whose pCO_2 does not fall below 75 Torr despite optimal medical management do not qualify for ECMO. This protocol is followed by all attending Neonatologists within the group. Changes in management strategy over the study period are the focus of this analysis, including the use of iNO, ECMO, PGI_2, and milrinone. Current guidelines include recommendations for initiation of iNO and ECMO, but not for use of IV vasodilators. The decision to use PGI_2 or milrinone is dependent upon the attending Neonatologist. Echocardiographic evaluation for PHTN is used at our center. Criteria for determination of PHTN include presence of ventricular septal flattening, directionality of PDA shunt if present, and estimation of pulmonary artery pressures based on tricuspid jet regurgitation using the Bernoulli equation.

Study Design

In this retrospective cohort study, the primary outcome was death prior to discharge. For comparison, 4 Eras were identified:

- Era 1, prior to availability of iNO, ECMO, or PGI_2 and milrinone (1998–1999)
- Era 2, iNO available, pre-ECMO, pre-PGI_2 and pre-milrinone (2000–2002)
- Era 3, iNO and ECMO available, pre-PGI_2 and pre-milrinone (2003–2004)
- Era 4, iNO, ECMO, PGI_2 and milrinone available (2005-June 2013)

Statistical Analysis

Patient demographics were compared among the four Eras using a chi-square test or Fisher-Freeman-Halton test, as appropriate, for unordered categorical variables. For continuous variables, a one-way analysis of variance was used to compare the Eras, or a Kruskal-Wallis test if the variances were heterogeneous or the distribution notably skewed.

The morbidity outcomes of time on ventilator, time on oxygen, and age at discharge, each were continuous variables with right skewed distributions, so were modelled using multivariable generalized gamma regression models, with a log link and gamma family. [11, 12] Since the model is generalized linear model, when the data were back-transformed, the adjusted means, using marginal covariate adjustment, were ordinary arithmetic means, rather than geometric means. The four Eras were simultaneous compared using a Wald post-test on the adjustment means.

The mortality outcomes of mortality, not repaired, and survival for repaired, each binary outcomes, were modelled using multivariable logistic regression models. The adjusted percentages were computed from the models using marginal covariate adjustment. The four Eras were simultaneous compared using a Wald post-test on the adjustment means.

Mortality was also modeled using a multivariable Cox regression model as the primary statistical analysis. The proportional hazards assumption of the Cox models was tested for each covariate and globally using a significance test based on the unscaled and scaled Schoenfeld residuals. [13] All p>0.32, verifying the assumption was met. All models were fitted using the Stata-13.1 statistical software (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

Between 1 January 1998 and 30 June 2013, 260 infants with CDH were managed at our center. We excluded 68 as follows: diagnosis after 24 hours (n=17), major chromosomal (n=10) or severe congenital anomaly (n=18), initial management and operative repair at another hospital (n=7), and death within first few hours of life secondary to inability to stabilize or ventilate and/or parental request for no intervention (n=16). A total of 192 patients were included for analysis during the study period divided into the four Eras as follows: Era 1=21, Era 2=30, Era 3=22, and Era 4=119. Demographic data for patients are shown in Table 1. No significant differences were seen in gestational age, birth weight, gender, race, inborn status, prenatal diagnosis, sidedness of hernia or proportion of large defects (C or D by CDH Registry form) across Eras. Primary repair, a known predictor of increased survival, decreased over time but did not reach statistical significance (p= 0.10). [14] Additionally, gestational age and Caucasian race trended towards significance, because of this these variables were included in further analysis as potential confounders. The Wilford Hall/Santa Rosa (WHSR) clinical prediction score is a simplified formula with comparable area under the curve (AUC) values as the CDH Study Group algorithm for prediction of mortality. [4] A value greater than 0 indicates an 82% positive predictive value of survival, while a value less than 0 indicates an 88% negative predictive value for survival. In our cohort, a positive WHSR score decreased significantly over time (p = 0.008, Table 1). WHSR score was also included in further analysis as a potential confounder.

Management and Outcomes

When adjusted for potential confounders (gestational age, Caucasian race, primary repair, WHSR score) age at discharge for survivors trended towards significance over time (median = 32 days in Era 1 to median = 50 days in Era 4, p = 0.18; Table 2.There were no differences in ventilator days or days receiving oxygen. Overall survival for the 192 patients was 81%. All 15 patients who were not repaired died. Survival to discharge for patients who were repaired was 88%. When accounting for variables that represent disease severity using logistic regression, there was no apparent difference between Era's in the primary outcome of death prior to discharge (Table 3). Since its introduction to CDH management in 2000, iNO use increased from 38% of patients in Era 2 to 80% in Era 4. Our ECMO utilization rate (25%) is equivalent to that reported by the CDHSG registry. Use of milrinone has stayed relatively constant at 50%, while PGI_2 use has declined from 43% to 15%, data not shown.

Primary Outcome

The primary outcome of death prior to discharge home was analyzed with a multivariable Cox regression model, with a forward variable selection rule that included a covariable in the model if it changed the hazard ratio of any Era variable by at least 10%.[15] Covariables included in the model were: primary repair, additional minor anomalies, and WHSR score. Covariables not included in the model were: gestational age, birth weight, gender, and prenatal diagnosis. There was no difference in hazard ratios across the four eras for mortality (Table 4).

Post-Hoc Analysis

Our results suggested a sicker cohort of patients over time with lower WHSR scores, less primary repairs in Eras 3 and 4. We postulated this may be a reflection of becoming an ECMO center in Era 3, with more severe infants in Era's 1 and 2 referred elsewhere prenatally. Subsequently, we evaluated the results as pre-ECMO (1998–2002) and ECMO (2003–2013). In this post-hoc analysis, the hazard ratio (HR) was 0.27, suggesting a 73% reduction in risk of death in the ECMO Era compared to pre-ECMO Era ($p < .001$; Table 5).

DISCUSSION

Congenital diaphragmatic hernia remains a challenging problem. In the modern era, despite new therapeutics to treat PHTN and advanced surgical techniques, the mortality rate remains stagnant. [16] Many centers have instituted standardized treatment protocols with some evidence of improved outcomes. [17–19] Such protocols typically include gentle ventilation and a non-emergent approach to operative repair, two interventions associated with improved survival in CDH patients. [3, 5] When adjusted for severity of illness, our results demonstrated an improved survival rate, associated with the availability of ECMO. However, in this same period of time, written CDH management guidelines were implemented. The introduction of protocols which focus on gentle ventilation have uniformly been associated with reported improved survival rates, this may play a role in the improved survival we have shown. [5, 18–19]

An improved understanding of pathways by which vascular smooth muscle cell relaxation occurs has recently led to increasing use of vasodilator therapies in our center. INO and sildenafil promote pulmonary vasculature dilation through increased intracellular cyclic GMP (cGMP) concentrations, whereas milrinone and PGI_2 enhance vasodilation by increasing intracellular cyclic AMP (cAMP). The apparent time related improvement in survival of a more severe cohort of CDH patients may, in part, be related to more effective management of PHTN through the combined use of multiple therapies. However, this retrospective study is neither designed nor powered to support this conclusion; more rigorous studies are needed.

There are several limitations to our study. It is retrospective in nature and none of the interventions included were applied as part of any randomized trial. A selection bias may exist for the first two Eras, prior to becoming an ECMO center when more severe infants may have been referred elsewhere. Additionally, 80% of all large defects were managed

during Eras 3 and 4. [16] We attempted to control for this by controlling for primary repair as a surrogate to defect size and severity. Additional confounders that cannot be controlled for include surgeon experience as well as Neonatology attending decisions regarding treatment strategies.

Additionally, the first 3 Eras were relatively short in comparison to Era 4, an issue we partially dealt with through the post-hoc analysis. A strength of our study is the relatively large number of patients seen at an individual institution.

CONCLUSION

Mortality remains high in the CDH population. Post-hoc analysis suggests an apparent improvement in survival in the ECMO Era, which included vasodilator therapies. Prospective studies are required to better understand the individual and combined effects of these treatment approaches on survival. Given the relative infrequency of the disease, collaboration among institutions will be necessary.

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Table 1

Demographic and clinical characteristics of infants divided by Era

	Era 1 (N=21)	Era 2 (N=30)	Era 3 (N=22)	Era 4 (N=119)	P Value
Gestational age (wk) *	37.8 (1.7)	37.5 (2.3)	38.3 (1.7)	37.5 (2.7)	0.12
Birth weight (gm) *	2898 (563)	2910 (726)	3119 (526)	2954 (650)	0.24
Male	14 (61%)	17 (53%)	15 (65%)	84 (65%)	0.62
Race					0.12
Caucasian	20 (87%)	27 (84%)	23 (100%)	104 (80%)	-
Other	3 (13%)	5 (16%)	0 (0%)	26 (20%)	-
Inborn	14 (61%)	18 (56%)	12 (52%)	76 (58%)	0.93
Prenatal diagnosis	14 (61%)	17 (53%)	12 (52%)	79 (61%)	0.78
Left sided hernia	21 (91%)	27 (84%)	20 (87%)	111 (85%)	0.78
Defect size C or D	6 (40%)	11 (41%)	13 (59%)	51 (44%)	0.55
Primary repair	15 (88%)	19 (73%)	15 (68%)	67 (60%)	0.10
WHSR score positive	20 (87%)	25 (83%)	18 (82%)	80 (62%)	**0.008**

* Mean (SD); all other data as number (%), WHSR= Wilford Hall Santa Rosa score

Era 1=1998–1999, Era 2=2000–2002, Era 3=2003–2004, Era 4=2005–2013

Table 2

Morbidities for infants divided by Era (limited to infants who survived)

	Era 1998–1999 (N=16)	Era 2000–2002 (N=22)	Era 3 2003–2004 (N=21)	Era 4 2005–2013 (N=97)	P Value
Unadjusted Descriptive Statistics, median (IQR*)					
Ventilator (days)	9 (4, 15)	9 (5, 14)	15 (8, 24)	9 (6, 23)	
Oxygen (days)	20 (10, 28)	16 (10, 32)	39 (26, 44)	22 (14, 58)	
Discharge age (days)	24 (15, 28)	26 (17, 39)	40 (26, 54)	37 (22, 68)	
Multivariable Gamma Regression Adjusted Mean (95% confidence interval)**					
Ventilator (days)	14 (8 – 20)	14 (9 – 19)	19 (12 – 26)	15 (12 – 18)	0.55
Oxygen (days)	28 (14–41)	33 (19–47)	43 (24–61)	39 (30–47)	0.49
Discharge age (days)	32 (19–44)	42 (27–56)	48 (32–64)	50 (42–57)	0.18

* IQR = interquartile range (25th and 75th percentiles)

** Adjusting for gestational age, Caucasian race, primary repair, and WHSR score positive, P value is from a regression post-test comparison of the equality of the four adjusted means. Each row represents a separate model.

Table 3

Mortalities for infants divided by Era

	Era 1 1998–1999 (N=21)	Era 2 2000–2002 (N=30)	Era 3 2003–2004 (N=22)	Era 4 2005–2013 (N=119)	P Value
	Unadjusted Count (percent)				
Mortality incidence	5 (24)	8 (27)	1 (5)	22 (18)	
Not repaired incidence	4 (19)	4 (13)	0 (0)	7 (6)	
Survival for repaired incidence*	16/17 (94)	22/26 (85)	21/22 (95)	97/112 (87)	
	Multivariable Logistic Regression Adjusted Percent (95% Confidence Interval)**				
Mortality incidence	23 (3–42)	25 (11–38)	6 (0–16)	10 (6–15)	0.20
Not repaired incidence	29 (9–50)	18 (4–33)	--***	5 (2–9)	**0.01**
Survival for repaired incidence	80 (59–100)	74 (59–88)	94 (84–100)	90 (85–94)	0.19

* Survival (not Mortality) in repaired patient subgroup

** Adjusting for candidate covariates gestational age, Caucasian race, primary repair (except not repaired outcome), and WHSR score positive, although only WHSR score positive remained in final models. P value is from a regression post-test comparison of the equality of the four adjusted percentages.

*** Zero percent after adjustment for covariates, so could not be estimated.

Table 4

Multivariable Cox regression model for mortality

	Hazard Ratio	95 % Confidence Interval		P
Era 1	1.00	-	-	-
Era 2	0.98	0.10	9.81	0.98
Era 3	0.21	0.01	3.9	0.29
Era 4	0.29	0.03	2.80	0.29

Controlling for primary repair, additional minor anomalies, and WHSR score. Variables considered but omitted from final model included Caucasian race, gestational age, birth weight, gender, and prenatal diagnosis.

Era 1=1998–1999, Era 2=2000–2002, Era 3=2003–2004, Era 4=2005–2013

Table 5

Post hoc analysis of combined Eras': Multivariable Cox regression model mortality outcome

	Hazard Ratio	95 % Confidence Interval		P
Pre-ECMO	1.00	-	-	-
ECMO	0.27	0.14	0.52	**<0.001**

Controlling for primary repair, additional minor anomalies, and WHSR score. Variables considered but omitted from final model included Caucasian race, gestational age, birth weight, gender, and prenatal diagnosis.

Pre-ECMO= 1998–2002, ECMO= 2003–2013