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Outcomes in the physiologically most severe congenital diaphragmatic hernia (CDH) patients: Whom should we treat?

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ABSTRACT

Purpose: Centers that care for newborns with congenital diaphragmatic hernia (CDH) may impose selection criteria for offering or limiting aggressive support in those patients most severely affected. The purpose of this study was to analyze outcomes in newborns with highly severe CDH uniformly treated for survival.
Methods: We reviewed 172 consecutive inborn patients without associated lethal anomalies treated at a single institution with a dedicated CDH program. Survival, respiratory outcome, and time to discharge in the most severe 10% (or fewer) of patients based on the physiologic measures of 5-minute Apgar, CDH Study Group (CDHSG) predicted survival, need for ECMO in the first 6 hours, and need for ECMO in the first 3 hours of life were studied. We also identified patients with best $PaCO_2$ greater than 100 and best pH less than 7.0. A multivariate model (AUC-0.92) predicting mortality was also used to define the most severe 10%.
Results: Of 172 consecutive inborn patients, 18 had a 5-minute Apgar of 3 or less, and 11 survived (61%), 10 had a 5-minute Apgar of 2 or less, and 6 survived (60%), and 6 had a 5-minute Apgar of 1 or less, and 4 survived (67%). Seventeen had a CDHSG predicted survival less than 25%, and 9 survived (53%). Thirteen of 172 required ECMO for rescue in the first 6 hours of life, and 9 survived (69%), including 7 in the first 3 hours, and 5 survived (71%). Despite focused resuscitation in the delivery room and high levels of ventilatory support, 22 patients had a best PCO_2 greater than 100 and best pH less than 7.0 for 1 hour or longer. Twelve of these 22 survived to discharge (55%). Of 17 defined by multivariate predictive modeling as the most severe, 8 survived (47%) with zero of the 3 ECMO ineligible prematures surviving. Of the 16 (10%) most severe ECMO-eligible patients, 10 of 16 survived (63%). All survivors were discharged home on no ventilatory support greater than nasal cannula oxygen.
Conclusion: In newborn CDH patients without lethal associated anomalies, accepted measures of physiologic severity failed to predict mortality. Survival met or exceeded 50% even in the most severe 10% as defined by these measures. These data support the practice of treating each patient for survival regardless of the physiologic severity in the first hours of life, and selection criteria for not offering ECMO should be reevaluated where practiced.

Congenital diaphragmatic hernia (CDH) is a severe and potentially life-threatening birth defect, with a wide spectrum of physiologic severity, and outcomes [1]. With widespread improvements in care based on lung preservation strategies [2–5], neonates with less severe CDH routinely survive in most centers, and newborns with more severe CDH survive at increasing rates at the best centers. Significant questions remain, however, about the viability and outcome potential of those most severely affected by the physiologic ravages of CDH [6,7].

As overall mortality in centers which measure CDH survival averages greater than 30% [8], it follows that mortality in those most severely affected will be much greater, possibly approaching 100%. Although documentation of such practice in the literature is rare, centers may apply arbitrary criteria for not offering aggressive treatment, especially escalating care to ECMO, for those infants felt to represent that most severe end of the spectrum [9].

Physiologic measures in CDH patients at birth and soon after have been shown to correlate with survival and include 5 minute Apgar score, birth weight, CDH Study Group predicted survival, and initial blood gas values [8,10,11]. Inborn versus outborn status also affects measured survival at the receiving centers, as the most severe outborn patients are less likely to be transported, or to survive transport, resulting in a selection bias toward less severity at the receiving center [6]. Further, outborn patients are less likely to be prenatally diagnosed resulting in less optimal resuscitation, which raises questions about the predictive value of the physiologic data gathered in the first hours for these patients. Finally, prenatal terminations may truncate CDH severity in geographic areas where such activity is significant.

Analysis of the severe end of the CDH spectrum would therefore be best represented by studying inborn patients from a center where prenatal terminations are minimal or nonexistent. To this end we studied our series of inborn patients with CDH, many of whom traveled significant distance after declining termination elsewhere, and who were treated aggressively for survival. We sought to define survival, time to discharge, and respiratory status at discharge, to address the question

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of whether treatment should be withheld from those with the highest severity CDH as defined by physiologic derangements at birth.

1. Methods

This is an IRB approved retrospective review of consecutive patients with congenital diaphragmatic hernia treated at UF Health, Shands Children's Hospital between September 1992 and December 31, 2011. A total of 268 consecutive CDH patients were identified from the cross reference of two separate medical record queries with operative records, autopsy records, a divisional database, and 2 prenatal evaluation databases. Patients with Morgagni CDH, diaphragmatic eventration, and patients in whom the diagnosis of CDH was missed and delayed more than 48 hours after delivery were not included. All patients were symptomatic in the first 6 hours of life. Of this total, 28 (10%) were judged to have lethal associated anomalies [12]. Of the remaining two hundred and forty, 172 were inborn and treated aggressively for survival, comprising the subjects of this study.

2. Clinical care

The majority of patients were prenatally diagnosed and counseled at our facility. Many had been offered pregnancy termination before our evaluation, but no parents chose termination for CDH alone after our evaluation. All patients included were treated with intent to cure regardless of clinical severity, utilizing strict limitation of ventilation pressures, avoidance of hyperventilation, and use of mild sedation as previously described [3]. Medical oversight throughout the series was uniform, leading to a high degree of therapeutic consistency.

For prenatally diagnosed patients, delivery was planned to occur between 38 and 39 weeks when possible, either by attempted induction or repeat cesarean section. EXIT, and EXIT to ECMO procedures were not used. Preterm labor was treated with attempt to attain at least 34 weeks gestation when clinically appropriate, but not always achieved. The attending pediatric surgeon and neonatal team were present at delivery, and intubation was accomplished immediately following delivery whenever prenatal diagnosis had been made. Apgar scores were assigned by the neonatal team.

Initial ventilation was pressure limited with Ambu bag or similar, utilizing peak inspiratory pressures of 20–25 cm of H20. Ventilator IMV rate was initially assigned at 50, 60, 80, or 100 breaths per minute based on best bedside analysis of clinical severity. Ventilation rates of 80 or higher were used for patients with severe physiologic compromise after birth defined by poor excretion of CO_2 as noted by delayed colorimetric change at initial intubation, 5 minute Apgar of 3 or less, and/or preductal saturations less than 70% despite successful intubation and ventilation with 100% oxygen. High frequency oscillation was used for premature CDH patients less than 32 weeks, and occasionally for nonprematures who failed to respond to conventional ventilation.

ECMO was used only for critical instability of preductal saturations, and only after employing all available modalities to avoid ECMO (pressors, nitric oxide, steroids, and intravenous pulmonary vasodilators). Initial ECMO was venovenous (VV) or venoarterial (VA) but with a preference for VA ECMO in the highest severity patients as judged by anatomic severity, physiologic severity, LHR, and blood gas values. Management on ECMO was not considered different from standard and has been previously described [10].

Data collected and used for this analysis include gestational age, birth weight, Apgar scores at 1 and 5 minutes, CDH Study Group Predicted Survival [11], and postductal blood gas values drawn as close as possible to 1 hour of life from an umbilical artery catheter. Laboratory analysis of blood gases changed from central laboratory to point of care during the experience. Partial pressure carbon dioxide measurements (PCO_2) were reported as greater than 130 mm Hg or greater than 100 mm Hg by the different systems, limiting the statistical analysis of very high PCO_2 values. Ventilator settings were analyzed as well as data regarding use of ECMO, timing of ECMO initiation, and survival. Time to discharge was also collected, as well as respiratory status at discharge.

3. Analysis

Independent variables of physiologic severity were analyzed independently and in multivariate logistic regression to assess effects on survival.

We used the R statistical software package. Fisher's exact test was used to compare the survival groups on categorical variables and Mann–Whitney tests to compare them on continuous variables. Survival based on the worst (roughly) 10% of patients for each individual severity variable tested is reported.

To develop a best-fit multivariate model that correlated most strongly with mortality, we used logistic regression utilizing the severity variables, and employed stepwise variable elimination based on the Akaike Information Criterion. The best-fit model's predictive ability was assessed using the area under the receiver operating characteristic curve (AUC). This multivariate model was then used to identify the most severe 10%, both including and excluding ECMO eligible infants, and using 33 weeks and 1800 grams to define eligibility.

4. Results

Of the total 172 consecutive inborn patients treated for survival that were without associated highly severe or lethal associated anomalies, 150 survived to discharge (87%). Eight of these were not eligible for ECMO support based on gestational age or size. Four of these eight did not survive, 3 of who met multiple measures of highest severity. Of the remaining 164 who were eligible for ECMO, 146 survived (89%).

Analyzing all 172 patients, highly significant relationships to survival existed for gestational age, birth weight, 1 minute Apgar, 5 minute Apgar, CDH SG predicted survival, need for ECMO, pH at 1 hours, PCO_2 at 1 hour, and (postductal) PO_2 at 1 hour (Table 1). The significance of the relationship was strongest for Apgar-1, Apgar-5; CDH Study Group predicted survival, first pH and first PCO_2. Time to ECMO in those patients needing ECMO support did not correlate with survival.

To understand the predictive value for mortality of individual poor results for the physiologic variables defined above, we looked at the survival of patients who had values in the lowest 5–10% of the total for those variables. These are reported in Table 2.

Logistic regression variable elimination algorithm was performed to develop a multivariate model of mortality based on the strongest individual predictive variables. Of these physiologic variables, the algorithm selected Apgar-1; CDH Study Group predicted survival (which includes Apgar-5 and birth weight), and pH at one hour. This resulting model had an AUC of 0.922 (Fig. 1). The 90th percentile of the model identified the physiologically most severe 10% of patients ($n = 17$ of 172) which included 3 prematures not eligible for ECMO. Eight of 17 survived (47%) and all 3 non-ECMO eligible prematures died. We then developed a model removing the 8 non-ECMO eligible prematures (AUC = 0.914)). Of 164 ECMO eligible CDH patients, the model defined the worst 10% ($n = 16$) and 10 of these survived to discharge (63%). The clinical characteristics of these patients are reported in Table 3. Nineteen patients are reported. The first 17 represent the physiologically worst 10% of the total 172, and the remaining 16 after removing the prematures from the 19 listed represent the most severe 10% ($n = 16$) of the remaining 164 ECMO eligible patients.

Mean time to discharge for survivors from the most severe 10% ($n = 17$) was 3.25 months with a range of 1.6–4.2 months. All patients