RESEARCH PAPER

Predictors of Mortality among Neonates with Congenital Diaphragmatic Hernia: Experience from an Inborn Unselected Cohort in India

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Objective: To evaluate the clinical profile and predictors of mortality in neonates with congenital diaphragmatic hernia (CDH). **Method:** Demographic and clinical parameters of neonates with congenital diaphragmatic heria (*n*=37) between January 2014 and October, 2017 were reviewed, and compared among those who survived or expired in hospital. **Result:** Median (range) gestation and birthweight were 38 (37-39) weeks and 2496 (2044-2889) g, respectively. Persistent pulmonary hypertension (PPHN) was documented in 19 (51%) neonates and 10 (27%) had associated malformations. Surgery could be performed in 18 (49%), overall mortality was 60%. On univariate analysis, low Apgar scores, presence of malformations, PPHN, need for higher initial peak inspiratory pressure/high frequency ventilation, and requirement of a patch for closure were associated with increased mortality. On multivariate analysis, PPHN remained the only significant risk factor [adjusted RR 3.74 (95% CI 1.45-9.68)]. **Conclusion:** The survival of infants with CDH is low, and PPHN is an important predictor of mortality.

Keywords: *Congenital malformation, Management, Outcome, Pulmonary hypertension*.

Congenital diaphragmatic hernia (CDH) affects 1 in 2500-3000 live births [1].The management of a neonate with CDH is challenging. Despite improvement of health care, mortality still exceeds 30% and morbidity among survivors is high. Overall survival is highly variable; varying from 70-80% in developed countries [1-4] and 38-72% in low- and middle-income countries [5-10].

Many neonates with CDH are not diagnosed in the antenatal period, and may die soon after birth and thus may not come to medical attention. These cases contribute to a significant "hidden" mortality. The clinical profile and outcome reported from out-born units and surgical units may under-estimate the actual mortality among CDH cases. The neonates who finally reach referral centers have lesser severity with relatively better prognosis. The actual burden is of the "hidden mortality" of the disease [2,11]. Hence this study was planned to describe the clinical profile and evaluate the outcome of neonates with CDH in an inborn neonatal unit.

Methods

Data from 37 consecutive neonates with CDH delivered at the All India Institute of Medical science, New Delhi between January, 2014 and October, 2017 was retrieved and analyzed from the hospital database. Neonates delivered elsewhere and transferred to the neonatal intensive care unit (NICU) or pediatric surgical unit were excluded. Data on demographic variables, treatment, and perioperative and postoperative outcomes of enrolled cases were collected using standard predesigned proforma.

Antenatally diagnosed cases of CDH were booked in obstetrics unit and underwent comprehensive prenatal evaluation which included ultrasonography and/or magnetic resonance imaging (MRI) for confirmation of diagnosis, assessment of severity and associated malformations. However, such an extensive evaluation was not possible amongst late referrals.

Delivery room management included involvement of at least two skilled personnel, elective intubation, and the use of T-piece resuscitator for positive pressure ventilation. Postnatal ventilatory management in the NICU utilized lung-protective strategy with conventional ventilation with time-cycled, pressure-limited ventilation (***Web Fig.* 1**). Inspired oxygen concentration (FiO_2) was adjusted to target pre-ductal oxygen saturation of >85%. Permissive hypercapnia ($PaCO_2$ 55-65 mmHg) was tolerated as long as pH was ≥7.25. If hypercapnia persisted on conventional ventilation or when PIP

required to target the desired $PaCO_2$ levels exceeded 20-25 cm H_20, neonates were switched to high frequency oscillatory ventilation (HFO). Persistent pulmonary hypertension was clinically suspected when there was labile oxygen saturation (SaO_2), pre-ductal SaO_2 <85% despite high FiO_2 or pre-post ductal difference in oxygen saturation of >10%. Echocardiography was performed in all cases to confirm PPHN, evaluate myocardial function and to rule out cardiac malformation. We used inhaled nitric oxide (iNO) in a few cases as a bridge to surgery or prior to considering the use of extracorporeal membrane oxygenation (ECMO). ECMO was used in two cases due to the presence of significant hypoxia (oxygenation index >40) and/or persistent hypotension/acidosis despite optimal ventilation and management of pulmonary hypertension. The management protocol, including supportive therapy, have been outlined in ***Web Fig.*1**.

Surgical repair was done when the neonate was clinically stable for at least 24 hours. Clinical stability was defined as ventilatory parameters of FiO_2 requirement of <60%, MAP <12, PaO_2 >50 mm Hg, normal blood pressures with minimum inotropic support (dopamine and/or dobutamine of ≤10 μg/kg/min) and urine output >0.5 mL/kg/hr). Repair was either primary or patch repair based on the size of the defect.

Statistical analysis: Patient demographics and hospital course were summarized and compared among those survived and died, in hospital. We used Fisher-exact test for categorical variables and Student t-test for continuous variables. Statistical analysis was done using Stata v 13.0 (Stata Corp, College Station, TX). For multivariate analysis, generalized linear model equation was used.

RESULTS

Of the 9,712 live births during the study period, 37 neonates (62% males) with diagnosis of CDH were included in the analyses. The median (IQR) gestational age and birthweight of the cases were 38 (37-39) week and 2496 (2044-2889) grams, respectively. Ultrasonographically, lung-head ratio (LHR) was documented only in 13 (35%) cases. Majority of (34, 92%) hernias were left sided and one baby had bilateral abnormality. Associated congenital malformations were noted in 10 (27%) cases, *viz* hypoplastic left heart with bilateral hydronephrosis, hemivertebrae, pulmonary sequestration, Dandy Walker malformation, bilateral corneal opacity, single kidney, polydactyly and cardiac anomalies. The other perinatal characteristics and resuscitation details are provided in ***Table* I**.

All cases requiring ventilatory support were initiated on conventional ventilation and about a half (*n*=14) were put on high frequency mode (HFO) subsequently. The median (IQR) initial and maximum peak inspiratory pressures in conventional mode were 17 (15-20) and 19 (15-21) cm H_2O, respectively. Median oxygenation index (OI) when HFO was initiated was 21 (14-45.75). Pneumothorax was noted in 11 (30%: 6 cases before and rest secondary to surgery) cases and PPHN in 19 (51%) cases: out of which 7 were stabilised and operated. In 13 neonates (35%) with refractory PPHN, inhaled nitric oxide was used at a median age of 2 (0.25-7) days. Pulmonary vasodilator medications like sildenafil and milrinone were used in approximately one-third. The median duration of ventilation among survivors was 12 (5.8-15) days.

Surgical repair could be performed only in 18 neonates: in 14 cases at median age of 2 days (IQR 1-5.7), while in rest at or beyond 2nd week. Closure of diaphragmatic defect was primary in 14 (78%) neonates while a patch was used in the rest (*n*=4). Extracorporeal membrane oxygenation (ECMO) support was used in two cases on day 14 and 17, respectively during primary repair: both cases succumbed due to multi-organ dysfunction. One case of left sided CDH, with persistent ventilatory requirement and repeated extubation failure after surgical repair improved after repair of a diaphragmatic hernia on the contralateral side, detected later.

TABLE I DEMOGRAPHIC CHARACTERISTICS, RESUSCITATION DETAILS AND POSTNATAL COURSE (*N*=37)

Characteristics	*N (%)*
Antenatal diagnosis	33 (89)
Vaginal delivery	31 (83)
#GA at diagnosis (wk)	25 (23-29.8)
Respiratory distress requiring intubation in delivery room	36 (97.3)
Chest compression during delivery room resuscitation	4 (10.8)
Fluid bolus during resuscitation	8 (21.6)
#Apgar score (1 min)	4 (2-6)
#Apgar score (5 min)	7 (5-8)
Primary repair	18 (48.6)
Age of repair (d)	4.8 (2.9-4.8)
Incidence of PPHN	19 (51.3)
HFO	20 (54)
#Maximum MAP	14 (11-17)
Need for ECMO	2 (5.4)

HFO: High frequency oscillation ventilation, MAP: mean airway pressure, PPHN: persistent primary pulmonary hypertension, ECMO: extra corporeal membrane oxygenation; #Median (IQR).

In our cohort overall mortality was 59.5%; 51% (19/37) died before surgical correction and 8% (3/37) died post-operatively. Univariate analysis was carried out for sex, laterality of lesion, co-morbid malformations intubation in delivery room, chest compression in delivery room, fluid bolus, APGAR scores, cord pH, initial PIP, need for HFO, age at surgery, duration of hospital stay, PPHN, shock, sildenafil use, milrinone use, inhaled NO use, use of antibiotics, sepsis, and use of patch for closure (***Table* II**). The following factors were associated with increased mortality: low 1 and 5 minute Apgar scores, higher initial PIP requirement on conventional ventilation, associated congenital malformations and PPHN. Requirement of a patch repair was associated with an increased risk for mortality relative to primary repair (100% *vs*. 6.67%, $P = 0.005$). On multivariate analysis using generalized linear model with mortality as dependent variable and factors that were considered to be clinically important (gestation, birth weight, malformation, Apgar score at 5 min and PPHN) as independent variables; only PPHN was associated with a higher mortality with adjusted risk ratio of 3.74 (95% CI 1.45-9.68) (***Table* III**).

DISCUSSION

The overall mortality among CDH cases born in our centre was 59% and the presence of PPHN was a significant predictor. We followed a protocol based management with lung protective ventilation, permissive hypercapnia, and elective surgical repair. There is paucity of reports from the LMICs regarding the outcomes of CDH patients [5-10].

The differences in survival when compared to the developed world can be attributed to factors like lack of a dedicated CDH team, absence of any hidden mortality in current cohort (ours was an unselected population of all inborn neonates). In general, population-based studies have reported lower survival than studies from single institution; this difference being due to the presence of a 'hidden' mortality [12,13]. Skari, *et al*. [14] noted that prenatal diagnosis of CDH, associated major malformations, side of hernia and study population had a major influence on mortality. Therefore, these factors should be taken into consideration while interpreting survival outcomes from various studies. Ours was an unselected population which included all in-born neonates irrespective of associated malformation and laterality.

Only few studies have reported postnatal risk factors for poor outcomes in CDH neonates in LMICs [5–8,10]; most of them are from outborn and from referral units, thus leading to a selection bias. The poor prognostic factors include established antenatal diagnosis, intramural birth, and presence of an associated malformation, PPHN and absence of a hernia sac in intraoperative findings. PPHN was the most important determinant of survival in our study similar to previous studies [6,15,16].

We used ECMO in two cases as a bridge to surgical repair. Low utilisation of ECMO has been reported even from large surgical centres in Europe [17]. The centres following preoperative medical stabilization with selective use of ECMO followed by surgical repair have reported higher survival [3,13,18], when compared with facilities not using ECMO [19,20].

In this cohort, we screened for associated malformations using echocardiography, ultrasonography,

TABLE II SIGNIFICANT PREDICTORS OF MORTALITY AMONG BABIES WITH CONGENITAL DIAPHRAGMATIC HERNIA (*N*=37)

Characteristics	*Survived N= 15*	*Deaths N= 22*	*P value*
Malformation	1 (6.7)	9 (40.9)	0.03
#Apgar score at 1 min	6 (4-7)	2.5 (2-5.25)	0.01
#Apgar score at 5 min	8 (7-8)	6 (4-7.25)	<0.01
Initial PIP*	15.5 (14-16.25)	19.5(17-22)	<0.01
Need for HFO	5 (33.3)	15 (68.2)	0.04
Day of surgery	2(1-4)	14 (4-21)	0.03
Hospital stay (d)	20 (14-26)	4(2-14)	0.001
PPHN	1 (6.7)	18 (81.8)	<0.01
Sildenafil use	1 (6.7)	10 (45.5)	<0.01
Milrinone use	1 (6.7)	12 (54.5)	<0.01
Inhaled nitric oxide initiation	0	13 (59.1)	<0.01
Antibiotics	14 (93.3)	12 (54.5)	0.01
Patch for diaphragm closure (*n*=18)	1 (6.6)	3 (100)	0.01

*HFO: high frequency oscillatory ventilation, PIP: Peak inspiratory pressure, PPHN: persistent pulmonary hyppertension of newborn; *in conventional mode; #median (IQR).*

TABLE III MULTIVARIATE ANALYSIS FOR PREDICTORS OF MORTALITY (*N*=37)

Factor	*Adjusted Risk Ratio (95% CI)*	*P Value*
Gestation	0.96 (0.49-1.87)	0.91
Birthweight	0.99 (0.99-1.00)	0.86
Malformation	0.37 (0.06-2.15)	0.27
Apgar at 5min	0.78 (0.46-1.30)	0.34
PPHN*	3.74 (1.45-9.68)	< 0.01

**PPHN: persistent pulmonary hypertension of newborn.*

WHAT THIS STUDY ADDS?

- Presence of persistent pulmonary arterial hypertension is an important risk factor for mortality among CDH infants in developing countries.

karyotyping (in neonates with suspected syndrome on clinical evaluation) and autopsy (whenever parents consented). However, the outcomes reported from a limited study population and from a single center are limitations of this study. We did not have antenatal data pertaining to severity of CDH in many cases, due to late referral. Ours being a tertiary care centre, there could be a referral bias due to referral of complicated or severe cases diagnosed antenatally.

Management of CDH in developing world is still challenging. Our centre had a high mortality rate despite good neonatal intensive care and surgical management. PPHN was an important predictor of mortality.

Contributors: TS: developed study proforma, collected data and wrote the first draft of the paper; SS: collection of data and contributed in writing the manuscript; DT: collection of data and analysis of results; AV: give important inputs in conduction of study and writing of the manuscript; AT: supervised implementation of the study and corrected the final manuscript ad reviewed; JS: data analysis and compilation, writing up the final manuscript; RA,AD: supervised the study as well as gave critical inputs in writing up the manuscript.
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