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EXPERIENCE OF CONGENITAL DIAPHRAGMATIC HERNIA IN NEONATES IN A TERTIARY CARE HOSPITAL IN NORTH KARNATAKA, INDIA.

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Abstract:

Background: Congenital diaphragmatic hernia (CDH) is associated with significant morbidity and mortality. Survival rates for CDH neonates have increased with early prenatal detection and improved postnatal management.

Aims and Objectives: To assess the Clinical profile, Risk factors for mortality and Analyze the Predictors affecting the Outcome at discharge for neonates with CDH.

Materials and Methods: This was a retrospective study conducted over a period of 03 years in a tertiary care in North Karnataka, India. Clinical characteristics and risk factors of 15 neonates diagnosed with CDH were compared between survivors and non-survivors. Neonates with clinical and intra operative diagnosis of diaphragmatic eventration were not included in this study.

Results: A total of 15 neonates diagnosed with CDH were included. There was a significant difference between CDH neonates who survived (87%) and those who died (13%), in terms of onset of respiratory distress, preoperative ventilation, the presence of severe PPHN, maximum OI on day 1, surfactant administration, large defect size, intrathoracic liver, sepsis and length of hospital stay with ($P < 0.05$). The maximum OI on first day < 15 and absence of severe PPHN predicted the survival for CDH neonates. (P value<0.005).

Conclusion: The overall survival rate among CDH neonates in our institutional experience was good. Risk factors for mortality include onset of respiratory distress, maximum OI > 15 on first

day and need for preoperative ventilation. Maximum OI on first day < 15 and absence of severe pulmonary hypertension are good predictors of the survival for CDH neonates.

Key words: congenital diaphragmatic hernia, pulmonary hypertension, neonatal survival, outcomes.

Charki et al, Experience of Congenital Diaphragmatic Hernia in Neonates.

INTRODUCTION:

Congenital diaphragmatic hernia (CDH) is complex birth defect with multifactorial etiology and associated with significant morbidity and mortality. Vincent Bochdalek, first described CDH in 1848 and Gross in 1946 did the first successful repair of CDH in a neonate.[1] Till 1980, the standard of care was immediate surgical repair followed by postoperative stabilization. Over last two decades, it has been concluded that neonatal CDH is a medical emergency. Lung hypoplasia, primary pulmonary hypertension and the presence of other lethal anomalies contribute to high morbidity and mortality in CDH neonates. Harrison et al. stated that neonates with CDH reaching a tertiary care center commonly represent only 40%–50% of cases reflecting the unknown mortality of CDH.[2]

Over the last decade, reported survival rate has improved from 50% to around 85% for CDH neonates, but the situation varies in developing countries.[3-6] "CDH EURO" consortium has developed standardized guidelines for the management of CDH neonates in 2010 and recently updated.[7,8] Despite the advances in prenatal and neonatal care, the high mortality and morbidity for CDH infants prompt the researchers to study the predictors of outcome in CDH neonates.[9] Antenatal and postnatal predictors for survival in CDH neonates have been studies and both have the similar prognostic ability. Antenatal predictors involve markers for severity of lung hypoplasia and pulmonary hypertension.[10]

The postnatal predictors for CDH include score for neonatal acute physiology on first day, CDH composite score, Wilford Hall/Santa Rosa prediction formula and oxygenation index (OI).[11,12.] Antenatal predictors do not account for the postnatal adaptation of the baby. Simple predictor scores such as OI have easy bedside application, rather than complicated composite scores.[13] We carried out this study to assess the Clinical profile, Risk factors for mortality and Analyze the Predictors affecting the Outcome at discharge for neonates diagnosed with CDH during the period from June 2017 to May 2020 and to find the postnatal factors predicting their survival.

MATERIALS AND METHODS:

This was a retrospective observational cohort study conducted from June 2017 to May 2020 over a period of 3 years at a tertiary care neonatal referral center in North Karnataka, India. The data was collected from NICU medical records department and pediatric surgical department registry. **Inclusion Criteria:** Neonates from day 0 to day 30 referred with a clinical suspicion and antenatal diagnoses of CDH were included in this study. All neonates with suspected or antenatally diagnosed CDH were admitted in NICU and started on supportive care as per standard protocol. The diagnosis of CDH was made from chest roentgenography and ultrasonography. Contrast-enhanced computerized tomography (CECT) was done in doubtful cases if required. **Exclusion Criteria:** Neonates with diaphragmatic eventration and aged more than 30 days were excluded from this study.

Baseline investigations including Complete blood count, Arterial Blood Gas analysis and Echocardiogram was done on day 1 of NICU admission. Assisted ventilation was provided for neonates requiring ventilation both preoperatively and postoperatively as per unit protocol. Surgery was performed when the neonate's general condition improved and blood gases were stabilized for at least 24 h. Repair of CDH under general anesthesia was adopted as treatment modality after initial medical stabilization. The onset of respiratory distress was defined as the time of respiratory distress starting after birth of the neonate. Congenital cardiac malformations were diagnosed using two-dimensional (2D) echocardiography. Persistent pulmonary hypertension of the newborn (PPHN) was diagnosed by 2D echocardiography. The size of the diaphragmatic defect was determined by the operating surgeon at the time of procedure. Stabilization of neonate was defined by the following criteria (a) Normal hemodynamic parameters: Mean blood pressure >40 mmHg, Heart Rate- 120-160b/min, CFT<3 sec, Spo2- 87-95%(Preductal) (b) improvement in signs of PPHN clinically and on 2D echo (c) Minimal Pressure requirement (15–20 cm H_2O) while on Ventilation (Conventional Ventilation/ HFOV) and adequate oxygenation achieved with minimal oxygen requirement (≤0.6). Oxygenation Index (OI) was calculated by the following formula: (MAP × FiO_2 × 100)/Pre ductal O_2, where mean airway pressure (MAP) is MAP. FiO_2 is fractional inspired oxygen and P_aO_2 partial pressure of oxygen in arterial blood sample. Duration of mechanical ventilation was defined as the days of ventilation prior to surgery. The Institutional Ethics Committee has approved this study.

RESULTS:

A total of 15 neonates with CDH were enrolled in this study and underwent surgical procedures. Of 15 neonates, 13/15 (86.66%) survived and 2/15 (13.3%) neonates expired postoperatively. In our study, 10/15 (67%) were males and 05/15 (33%) were females with a male to female ratio of 2:1. Mean gestational age at birth of the survivors was 37.5 ± 01.20 weeks and 36.89±1.03 in non survivors. Mean birth weight of survivors was 2810 ± 450 g and 2570±340 in non survivors. Antenatal diagnosis of CDH was confirmed in 08(68%) survivors. 10/13(77%) of survivors were delivered by cesarean section whereas 01/02(50%) of non survivors. The mean hour of life that neonates were admitted was 40±14.6 among survivors and 39±15.8 among non survivors. Mean Apgar score at 1 min for survivors was 6.4 ± 0.8 and 6.1 ± 1.10 for non survivors. Mean Apgar score at 5 min for survivors was 8.5 ± 0.40 and 7.9 ± 0.90 for non survivors. 08/13 (62%) neonates with CDH had non lethal cardiac malformations among survivors and 01/02 (50%) among non survivors. In this study, none of the neonates had any lethal or cyanotic congenital heart diseases. Left sided CDH predominated with 13/15 (87%) and right sided CDH were 2/15 (13%). When comparison was made between survivors and non survivors of right sided and left sided CDH in neonates, we found both carried fairly good prognosis with a $P > 0.05$ which was not significant statistically. In our study, we did not encounter any neonate with bilateral CDH, Morgagni hernia or Larrey's hernia. The entire above mentioned baseline characteristics were not statistically significant. (P>0.005)(Table-1)

Table 1: Baseline Characteristics of Survivors and Non survivors among CDH Neonates.

Parameters	Survivors (*n*=13)	Non survivors (*n*=2)	*P* Value	Significance
Gestational age (weeks)	37.5 ± 01.20	36.89±1.03	0.518	NS
Birth weight (gms)	2810 ± 450	2570±340	0.487	NS
Age on admission (hr)	40±14.6	39±15.8	0.926	NS
Sex				
Male	09/13 (69%)	01 (50%)	0.591	NS
Female	04/13 (31%)	01(50%)		
Antenatal Diagnosis				
No	05(32%)	02(100%)	0.104	NS
Yes	08(68%)	00(00)		
Mode Of Delivery				
Normal Vaginal Delivery	03(23%)	01(50%)	0.423	NS
Cesarean Section	10(77%)	01(50%)		
1 min Apgar score	6.4 ± 0.80	6.1 ± 1.10	0.641	NS
5 min Apgar score	8.5 ± 0.40	7.9 ± 0.90	0.108	NS
Cardiac Malformation				
No	05 (38%)	01 (50%)	0.756	NS

Yes	08 (62%)	01 (50%)		
Side of diaphragmatic hernia				
Left	12 (92%)	01 (50%)	0.101	NS
Right	01 (08%)	01 (50%)		

Note: significant at 5% level of significance (p<0.05), NS- not significant, Sig- Significant.

Mean onset of respiratory distress in hours was 6.07 ± 1.04 (median 6.0, range 2–10) in survivors and 4.03±1.51 in non survivors (P<0.005). Severe PPHN was observed in 02 (15%) of survivors and 02 (100%) of non survivors (P<0.005). Maximum OI on day 1(>15) was documented in 2(15%) of survivors and 2(100%) in non survivors (P<0.005). Need of surfactant administration was stated in 2(15%) of survivors and 2(100%) in non survivors (P<0.005). 03/13(23%) of survivors and 02(100%) of non survivors required preoperative ventilation among which 02 (67%) required HFOV in survivors and 02(100%) in non survivors. Above mentioned parameters were statistically significant. (P<0.005) Inotropic Requirement was observed in 09(69%) in survivors and 02(100%) in non survivors which was not statistically significant (P>0.005).(Table-2)

Table 2: Comparison of Parameters in Survivors and Non survivors among CDH Neonates.

Parameters	**Survivors (*n*=13)**	**Non survivors (*n*=2)**	***P* Value**	**Significance**
Onset of respiratory distress hr	6.07 ± 1.04	4.03±1.51	0.027	Sig
Maximum OI on day 1(>15)	2(15%)	02(100%)	0.001	Sig
Surfactant				
No	11(85%)	0(00%)	0.001	Sig
Yes	02(15%)	02(100%)		
Inotropic Requirement	09(69%)	02(100%)	0.359	NS
Severe PPHN				
NO	11(85%)	00(00%)	0.001	Sig

Yes	02 (15%)	02 (100%)		
Pre operative ventilation				
No	10 (77%)	00 (00%)	0.032	Sig
Yes	03 (23%)	02(100%)		
HFOV				
No	01 (33%)	00 (00%)	0.36	NS
Yes	02 (67%)	02 (100%)		
Operation(24-72h)	60±6.4	68±5.1	0.059	NS
Large Defect size	03(23%)	02(100%)	0.032	Sig
Intrathoracic Liver	01(7.7%)	02(100%)	0.002	Sig
Pneumothorax	02(15%)	02(100%)	0.011	Sig
Sepsis	03(23%)	02(100%)	0.032	Sig
Length of Hospital stay (days)	20.84±4.4	13.42±3.1	0.042	Sig

Note: significant at 5% level of significance ($p<0.05$), NS- not significant, Sig- Significant.

Ventilation parameters showed statistically significant observations in CDH neonates. Max OI on Day 1 was 08 ±5.3 among survivors and 17±4.4 among non survivors (P=0.041). Max Fio2 needed on Day 1 was 0.50±0.1 among survivors and 0.9±0.1among non survivors (P<0.001). Max MAP required on first day was 8.30±1.4 among survivors and 11.38±2.5 among non survivors (P=0.018).(Table-3)

Table 3: Ventilation details of Survivors and Non survivors among CDH Neonates.

Parameters	Survivors (*n*=13)	Non survivors (*n*=2)	*P* Value
Max OI on Day 1	08 ±5.3	17±4.4	0.041(Sig)
Max Fio2 needed on Day 1	0.50±0.1	0.9±0.1	<0.001(Sig)
Max MAP required on first day	8.30±1.4	11.38±2.5	0.018(Sig)

Note: significant at 5% level of significance (p<0.05), NS- not significant, Sig- Significant.

Intra operative findings showed Large defect size in 03(23%) in survivors and 02(100%) in non survivors (P<0.005). Intrathoracic liver was documented in 01(7.7%) in survivors and 02(100%) in non survivors (P<0.005). Complications such as Pneumothorax were observed in 02(15%) in survivors and 02(100%) in non survivors (P<0.005). Sepsis was documented in 03(23%) in survivors and 02(100%) in non survivors (P<0.005). Mean length of hospital stay was 20.84±4.4 days among the survivors and 13.42±3.1 among non survivors (P<0.005). (Table-2)

There were a total of 2/15 (13.3%) deaths in our study. Among which 01/13 (7.6%) neonates with left-sided CDH died whereas 01/02 (50%) neonates with right-sided CDH died. Overall mortality was 13.3%. Univariate analysis comparing survivors and non survivors with CDH revealed that mortality was not associated with the following factors such as gestational age (weeks), birth weight (grams), gender, antenatal diagnosis, mode of delivery, Apgar score at 1 min and 5 min, age at admission, the presence of cardiac malformation and laterality with P > 0.05 which was not statistically significant.

However, mortality was associated with the following factors; onset of respiratory distress, preoperative ventilation, the presence of severe persistent pulmonary hypertension of the newborn (PPHN), maximum OI on day 1, surfactant administration, large defect size, intrathoracic liver, pneumothorax, sepsis and length of hospital stay with P < 0.05 which was statistically significant. The survival at discharge for CDH was 86.7% (13/15 neonates). We analyzed the absence of severe pulmonary hypertension, maximum OI on first day < 15, and absence of pneumothorax for predictors of survival (Table 4). The maximum OI < 15, severe pulmonary hypertension and absence of pneumothorax predicted the survival for CDH neonates with significant P value<0.005. The sensitivity and specificity for maximum OI < 15 on first day, to predict survival was 0.85 (confidence interval 0.52-0.99) and 1.00 (90-0.99) respectively.

Table 4: Predictors of survival in CDH Neonates

Parameters	Survivors (*n*=13)	Non survivors (*n*=2)	*P* Value
Maximum OI on first day < 15 n (%)	11(85%)	00(100%)	0.001(sig)
Absence of severe pulmonary hypertension	11(85%)	00(00%)	0.001(sig)
Absence of Pneumothorax	11(85%)	00(00%)	0.001(sig)

Note: significant at 5% level of significance (p<0.05), NS- not significant, Sig- Significant.

Sensitivity and Specificity of risk factors for mortality was assessed in CDH neonates. Onset of respiratory distress < 6 hours of life had sensitivity and specificity of 100% and 69% respectively with negative predictive value of 100%. Requirement of Preoperative ventilation had sensitivity and specificity of 100% and 77% respectively with negative predictive value of 100. Maximum OI on first day >15 had sensitivity and specificity of 100% and 85% respectively with negative predictive value of 100 %.(Table-5)

Table 5: Risk factors for mortality in CDH Neonates

	Onset of respiratory distress (<6hr)	Preoperative Ventilation	Maximum OI on first day >15
Sensitivity	100.00%	100.00%	100.00%
Specificity	69.23%	76.92%	84.62%
PPV	33.33%	40.00%	50.00%
NPV	100.00%	100.00%	100.00%
Accuracy	73.33%	80.00%	86.67%

DISCUSSION:

Over the last three decades, CDH has been recognized as a syndrome, which includes pulmonary hypoplasia, lung immaturity, left heart hypoplasia and PPHN of the newborn. Harrison et al. stated that neonates with CDH reaching a tertiary care center commonly represent only 40%–50% of cases reflecting the unknown mortality of CDH.[1,2] Mean gestational age in the present study among survivors was 37.5 ± 01.20 weeks and among non survivors was 36.89±1.03 with no statistically significant difference. The median age on admission was 40±14.6 hours in survivors and 39±15.8 in non survivors with no statistically significant difference. This study suggests that the non survivor group had lower Apgar scores compared to survivor group at 1 minute and 5 minutes with no statistically significant difference. The low 1 and 5 min Apgar scores have been said to be major independent predictors of mortality.[14]

Antenatal detection rate of CDH varies a lot in literature around 10% to 79%. However, it is less in developing countries due to inadequate antenatal visits and lack of facilities.[15] In our cohort, 53% of the cases were diagnosed antenatally. Polyhydramnios has been documented in up to 80% of CDH cases.[16] 3D estimation of the fetal lung volume, calculation of the right lung area to thoracic area ratio and calculation of the lung to thoracic circumference ratio has been the most widely used as antenatal prognostic indicators.[17,18]

Postnatally, CDH is usually diagnosed after birth with clinical signs of respiratory distress, scaphoid abdomen, bowel sounds in the chest.[19] Imaging modalities include Chest and Abdomen X ray, Ultra sonogram, Contrast Enhanced C T scan and barium meal follow through in doubtful cases.

In neonates with CDH, cardiac malformations are most common associated anomalies with unknown etiology. In this study, atrial septal defect, ventricular septal defect, and patent foramen ovale predominated in cardiac malformations (60%). The respiratory distress in CDH is due to two factors: pulmonary hypoplasia and pulmonary hypertension.[17] The onset of respiratory distress and the prevalence of PPHN with maximum OI >15 on first day were high risk factors related to the severity of clinical characteristics in CDH neonates. In this study, survivors presented with respiratory distress at 6.07 ± 1.04 hours of life where as non survivors presented with respiratory distress at 4.03±1.51 hours of life which was significant statistically.(P=0.027).

Degree of lung hypoplasia and PPHN correlated well with survival as well as morbidity in neonates with CDH. Lung hypoplasia is the major determinant of survival and the degree of pulmonary hypoplasia correlates with severity of PPHN.[20] In our study, 15% of survivor neonates had severe PPHN and among non survivors 100% had severe PPHN which was highly statistically significant ($P < 0.001$). 15% neonates with CDH in survivor group presented with maximum OI on first day >15 compared to 100% neonates with CDH in non survivor group which was significant statistically.(P=0.001). 15% neonates with CDH in survivor group required surfactant compared to 100% neonates with CDH in non survivor group which was significant statistically.(P=0.001).

The novel concept of gentle ventilation strategies which includes, preservation of spontaneous ventilation, permissive levels of hypercapnea ($PaCO_2$ 60–65 mmHg) and avoidance of high inspiratory airway pressures (> 25 cm H_2O) is being followed in our center.[21,22] In our institute, most of the neonates were managed by conventional ventilation as per standard protocol. In this study, 23% of the survivors received pre operative ventilation where as 100% of non survivors received pre operative ventilation which was significant statistically.(P=0.032)

CDH is no longer a surgical emergency. It is being acknowledged that stabilization of labile physiology is important followed by timely delayed repair in most of the surgical centers. Preoperative stabilization includes optimization of respiratory function in terms of gentle ventilation, management of severe PPHN followed by assessment of associated anomalies including cardiac assessment.

Surgical correction of CDH was generally performed through an upper transverse or subcostal abdominal incision. Minimally invasive approaches such as thoracoscopy and laparoscopy have been documented.[17,23] In our series, we operated on two right sided CDH cases through open surgical repair. Thirteen babies with left sided CDH underwent various surgical procedures including open surgical repair (10), thoracoscopic repair (2), in another one, laparoscopic procedure was attempted.

The size of the diaphragmatic defect has been shown to correlate well with mortality as well as morbidity in neonates with CDH. Defect size is likely to be an indicator for the degree of pulmonary hypoplasia. In this study, Large Defect size was observed in 23% of survivors and 100% of non survivors which was statistically significant ($P = 0.032$). Touloukian RJ et al, stated that defect size is not an independent predictor for mortality.[24] The presence of a hernial sac significantly improves the prognosis in CDH neonates which is formed of parietal peritoneum and

lung pleura and has been reported in approximately 20% of cases in the literature.[6] In our study, we found intraoperatively, the presence of sac in 13% neonates; all of them survived. With regard to the contents of organs in the chest cavity, the presence of intrathoracic liver is considered to be a poor prognostic indicator.[25] Albanese CT et al, has reported higher mortality among the neonates with right sided CDH with intrathoracic liver.[26] In our study, we found intrathoracic liver in 100% cases of non survivors and 7.7% cases of survivors which was significant statistically.(P=0.002).

Study by Usui *et al*., stated 14% incidence of pneumothorax among 510 neonates with CDH.[27] In our study, 15% neonates among survivors and 100% neonates among non survivors had preoperative pneumothorax which was significant statistically.(P=0.011). In this study, survivors (20.84±4.4 days) among CDH neonates had a longer NICU hospital stay compared to non survivors (13.42±3.1 days) which was significant statistically.(P=0.042). Similarly study by Schaible T et al,. stated increased duration of NICU stay in neonates with CDH who survived compared to non survivors.[28] Among the other associated conditions include an infection, acidosis, and neonatal jaundice which adds to the morbidity.[28] In this study, 23% neonates among survivors and 100% neonates among non survivors had sepsis which was significant statistically.(P=0.032). This result suggests that CDH neonates have a high morbidity and mortality rate in early life.

Right sided CDH is associated with higher mortality.[29] In this study, 13% of neonates with left sided CDH had mortality where as 50% of right sided CDH had mortality which was not statistically significant.(P=0.101). According to recent literature, the overall survival rate of CDH neonates in NICU ranges from 21% to 83%.[30,31] In this study, conducted over a period of 3 years, the survival rate among CDH neonates was 87%. Chandrasekaran *et al*., have reported on their 12 years' experience, survival of 78%.[32] Similarly, Panda *et al*. in their study reported survival of 61% for postoperative CDH neonates .[3] Jain *et al*. in their study reported survival of 87.5% for CDH.[33] Other studies from developing countries have shown the survival of 50%–65% for antenatal and Postnatally detected CDH neonates. Recent studies have shown better survival for isolated CDH up to 85%–90%, with improvement in standard protocols which involves the pulmonary hypertension management and availability of ECMO.[33]

Application of antenatal and postnatal predictors for CDH in neonates at bedside is difficult. Antenatal predicting scores do not consider postnatal cardio-respiratory adaptation after birth where as postnatal composite score is complex. OI is a marker of cardio-respiratory function of neonate and is widely used to assess the need for inhaled Nitric oxide in cases of severe PPHN and need for ECMO.[34] We found maximum OI on the first day of life as a good predictor of survival in CDH neonates with sensitivity of 100% and specificity of 69% at a cut-off of 15 to predict survival. In similar study from Poland, Basiewicz-Slaczka E et al,. reported sensitivity and specificity of 94% and 88% at cut-off of 12 for OI on first day.[35] Ali et al. found that the lowest OI on day 1 predicted survival in neonates with CDH.[36] Tan et al. in their study suggested that serial OI measurement is best predictor of the survival rather than single best OI.[37] In this study, absence of Severe Pulmonary hypertension and absence of preoperative pneumothorax were good predictors for survival with significant P value (0.001) Lusk LA et al,. stated that the presence of severe pulmonary hypertension and persistence of pulmonary hypertension also predict the short-term mortality and morbidity.[38]

In this study, we assessed the risk factors for mortality such as Onset of respiratorydistress<6 hours, need of preoperative ventilation and Maximum OI on first day >15 which were found to be

significant with negative predictive value of 100%. Similarly, Aihole JS et al., stated that the onset of respiratory distress and preoperative ventilation as significant risk factors for mortality in neonates with CDH.[39] The limitation of this study was that antenatal ultrasonography findings were not available in the medical case records.

CONCLUSION:

Despite the advancement in neonatal medicine, CDH remains a serious condition and its rate of morbidity and mortality remains high. We found a survival rate of 87% in CDH neonates using the standard protocol in management. Risk factors for mortality include onset of respiratory distress and need for preoperative ventilation. Maximum OI on first day <15 and absence of severe pulmonary hypertension are good predictors for survival. Approach to CDH has changed from immediate surgical repair to initial stabilization with aggressive management of pulmonary hypertension and delayed surgical repair. Prenatal and postnatal management of neonates with CDH is challenging in the best of centers and need multidisciplinary teams for most favorable outcomes. Survival rates for neonates with CDH has increased over the last decade with better management at resuscitation and stabilization, implementation of gentle ventilation strategies; and medical management of pulmonary hypertension and extracorporeal membrane oxygenation.

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