PREOPERATIVE RISK FACTORS FOR CONGENITAL DIAPHRAGMATIC HERNIA AMONG PATIENTS AT VIET NAM NATIONAL CHILDREN'S HOSPITAL

Tran Minh Dien[1], Pham Thi Thu Phuong[2]
Pham Hong Son[1]; Khu Thi Khanh Dung[1]
[1]Viet Nam National Children's Hospital;
[2]Ha Noi Gyneco-Ostretrics Hospital

ABSTRACT

Background: *Congenital diaphragmatic hernia (CDH) is a severe disease with a high mortality rate, especially in the postpartum period and neonates. Some risk factors are low birth weight, respiratory distress, cardiovascular failure, and coagulation disorder prevent the patients from receiving surgery, and deaths as a result.* ***Objectives:*** *To determine the preoperative mortality rate and risk factors for congenital diaphragmatic hernia among the patients at the Surgical Intensive Care Unit of the Viet Nam National Children's Hospital (VNCH).* ***Study methods:*** *Participants were the patients who had been diagnosed with neonatal congenital diaphragmatic hernias based on clinical symptoms and X-ray images of a hernia on the thoracic cavity from 1st January 2013 to 30th May 2015. These people were divided into two groups namely ineligible surgical and surgical indication. The variables included patients' characteristics (gestational age, admission age, and birth weight), clinical characteristics (respiratory distress, and hemodynamic parameters), and investigations. Data was analysed using SPSS 16.0.* ***Results:*** *There were 160 CDH patients participating in this study. Of that, 35 patients were ineligible surgery, followed by deaths, accounting for 21.9%. The risk factors that affected the ineligible surgical indication were hypothermia < 36^0 C (OR=7.18; 95% CI: 1.56 - 33.13); $PaCO_2$ > 60 mmHg (OR: 9.66; 95% CI: 2.73 - 34.19); Lactate > 2.5 mg/L (OR: 7.21; 95% CI: 2.11 - 24.60); pulmonary hypertension > 55 mmHg (OR: 15.36; 95% CI: 3.80 - 62.10); and platelets counter 150 000 G/L (OR: 7.69; 95% CI: 1.93 - 30.54). These factors were statistically associated with surgical indication after adjustment using multivariate analysis (p < 0.05).* ***Conclusions:*** *The rate of preoperative mortality among CDH patients, who were unable to receive surgery, was 21.9%. The risk factors when being hospitalized that prevented them from receiving surgery were the temperature < 36°C, $PaCO_2$ > 60 mmHg, pulmonary hypertension >55 mmHg, and platelets < 150,000 G/L.*

Key words: *Congenital diaphragmatic hernia, preoperative mortality, preoperative risk factors.*

Correspondent: Tran Minh Dien
Received: November 20th, 2018
Accepted: November 25th, 2018
Address: Email: dientm@nhp.org.vn

1. BACKGROUND

Congenital diaphragmatic hernia (CDH) is defined by the presence of an orifice in the diaphragm, more often left and posterolateral that permits the herniation of abdominal contents into the thorax. The incidence of CDH is about 1/2,000 - 1/5,000 live births [1,2]. The mortality rate of this disease is high, ranging from 20-60% depending on the country and clinical centers [3,4]. CDH is, therefore, a serious disease that contributes to an increase in the neonatal mortality rate.

Recent advances in the ultrasonic technology of prenatal diagnosis, anesthesia, resuscitation, and surgery have contributed to a significant decrease in the mortality rate of this disease. In addition, to reduce the mortality rate in CDH treatment, it is necessary to timely manage and properly resuscitate in the delivery room, as well as maintain artificial respiration when transferring the patients to the pediatric centers where are able to perform surgeries and give intensive care before, during, and after the surgeries [1,2,3,4]. Pediatricians must comply with the postnatal care strategies, including control of artificial ventilation with gentle ventilation to avoid lung injury, control of persistent pulmonary hypertension in the neonate, and delayed surgery until respiratory and cardiovascular system being stable [4].

According to some international reports, the preoperative mortality rate (ineligible for surgery) of CDH was about 10.8% to 21.0% [7,8,9]. Problems related not enough criteria for stabilization before surgery are low birth weight, congenital heart disease, chromosomal abnormalities, severe pulmonary hypertension, and cardiopulmonary collapses [4].

Every year, there were about 50-60 CDH patients going to the Vietnam National Children's Hospital (VNCH), and most of them are severe. More specifically, they suffered postpartum respiratory distress, circulatory failure, and severe pulmonary hypertension. Almost all studies focused on the patients who were able to receive surgery [5,6] or in other words, there is a lack of studies on preoperative clinical symptoms in the CDH patients. Therefore, it is very important to explore preoperative risk factors for CDH. This might enable the clinical doctors to give a better diagnosis for performing resuscitation and surgery. This study was conducted to (1) estimate the preoperative mortality rate of CDH and (2) identify preoperative risk factors for CDH among the patients of the Vietnam National Children's Hospital.

2. STUDY METHODS

2.1. Participants

All newborn babies with CDH who were hospitalized at the VNCH. Diagnostic criteria for CDH included (1) Clinical symptoms (respiratory distress with insufficient oxygenation, displacement of heart sounds to the contralateral side, excavated abdomen with sternal protrusion) and (2) chest X-ray as standard gold: bowel loops into the hemithorax, the mediastinum is displaced to the ontralateral side [1].

2.2. Study design

Retros- and pros-pective cohort study were conducted to collect data from 01/01/2012 to 30/06/2015 at the Surgical Intensive Care Unit (SICU), VNCH.

2.3. Sample size

A formula for calculating sample size for scale estimation: □

$$n = \frac{z^2_{1-\alpha/2}(1-p)}{\varepsilon^2 p}$$

Of which:

• n: the number of CDH newborns;

• Z1 - α / 2 = 1.96 at the level of confidence at 95%;

• p: the rate of preoperative mortality of 20% from previous studies;

• □: the relative precision estimated at 25%.

The needed sample size for this study was 144 patients.

2.4. Variables

A structured form was used to collect data in patients who statisfied with study selective criteria. The variables of preoperative risk factors were divided into two groups, including (1) continuous variables (mean ± SD): gestational age (months); weight birth (gram); admission age (days); PaO2 / FiO2 (mmHg); PaCO2 (mmHg); heart rate (bpm); mean blood pressure (MBP, mmHg); lactate (mg/l); pulmonary artery pressure (PAP) (mmHg); hemoglobin (g/dL); platelet (G/L); prothrombin (%); aPTT (seconds); pH; glucosemia (mmol/l); albumin (g/L); Ure (mmol/L); Creatinine (mcmol/L), and (2) categorical variables (n;%): male; mode of delivery (caesarean section); prenatal CDH diagnosis; postpartum intubation for respiratory distress; hypothermia below 36^0C; congenital heart defects (significant defects and non-significant defects); mechanical ventilation when being hospitalized;

Preoperative medical stabilization: (1) MBP >35-40 mmHg, urine output > 2 ml/kg/h, minimum inotrops. (2) oxygen sarturation ingradient between pre and post ductus arteries < 5%. (3) Conventional mechanical ventilation (CMV) or high frequency oscilization (HFO) to ensure safety with a value of peak pressure <25cmH_2O with CMV or a value of mean airway pressure < 17 cm H_2O with HFO.

2.5. Data analysis

Chi-square test was used to test the relationship between some categorical variables. OR and 95% confidence interval (95%CI) were given. Values of mean and standard deviation (SD) were calculated for continuous variables in case they are standard distribution variables. A t-test was used for these variables. Values of median, min, and max were reported for the variables that were not standard distribution. A non-parametric test was used in this situation.

Receiver operating characteristic curve (ROC) was developed to identify cut of points. If the area under the ROC curve was higher than 0.60, the continuous variables would be categorized based on the identifed cut of points.

Multivariate analysis using Stepwise method was developed to determine the relationship between some preoperative variables and CDH.

p-value at 0.05 was used to test for statistical significance.

3. STUDY RESULTS

There were 160 patients eligible for the study. Of which, 35 patients did not meet the criteria for stabilization before surgery (ineligible surgery), accounting for 21.9%. The median age of the study participants was 1 day, ranging from 1 to 28 days. Their average birth weight was 2.9±0.5kg. 30 patients (18.8%) received prenatal CDH diagnosis. Remarkably, 103 patients with respiratory distress (64.4%) were given tracheal intubation, and 26 patients (16.7%) had hypothermia upon admission. Additionally,

when admission, 134 patients (83.7%) with respiratory distress used the assist mechanical ventilations with the median PaO2/FiO2 ratio at the lowest value of 150 mmHg (min-max: 7-952 mmHg) and the median PaCO2 at a high value of 52 mmHg (15-115 mmHg). Signs of the cardiovascular system included an average heart rate of 141±20bpm; the MBP of 44 ± 11 mmHg, and lactate of 2.3 mg / l (0.5-15). The average PAP within 24 hours admitted was 46 ± 20 mmHg. There were 68 patients (44.2%) suffered the pulmonary arterial hypertension (PAH), among them there were 26 patients (16.9%) suffered at a severe PAH.

Results of some risk factors that do not meet preoperative criteria as follows: □

Table 1. Clinically epidemiological characteristics of the study group

	Surgery (n=125)	Ineligible surgery (n=35)	p-value
Male (n, %)	74 (59.2)	22 (62.9)	> 0.05
Mode of delivery: caesarean section (n, %)	37 (26.9)	11 (31.4)	> 0.05
Gestational age (weeks, mean±SD)	38.3 ± 1.8	37.3 ± 2.6	< 0.05
Birth weight (grams, mean±SD)	2950 ± 521	2614 ± 443	< 0.001
Age when admission (days, median (min-max))	1 (1-28)	1 (1.0-11.0)	< 0.01
Prenatal CDH diagnosis (n,%)	23 (18.4)	7 (20.0)	> 0.05
Postpartum intubation for respiratory distress (n, %)	73 (58.4)	30 (85.7)	< 0.01
Hypothermia (n,%)	11 (9.0)	15 (44.1)	< 0.001
Congenital heart defects (n, %)			
Non-Significance	45 (91.8)	16 (76.2)	> 0.05
Significance	4 (8.2)	5 (23.8)	

There were statistically significant differences in lower gestational age, lower birth weight, respiratory distress postpartum, and hypothermia between surgical and ineligible surgical groups (p< 0.05).

Table 2. Respiratory characteristics of patients admitted to hospital

	Surgery (n=125)	Ineligible surgery (n=35)	p-value
Types of breathing (n,%):			
Self breathing	10 (8.0)	0 (0)	< 0.01
Self-breathing with oxygen masks	17 (12.8)	0 (0)	
Mechanical ventilation	99 (79.2)	35 (100)	
PaO_2/FiO_2 (mmHg), median (min-max)	180 (20-952)	35 (7-387)	< 0.001
$PaCO_2$ (mmHg), median (min-max)	50 (15-115)	85 (29-115)	< 0.001

There were statistically significant differences in receiving mechanical ventilation, low PaO2/FiO2 ratio, and high PaCO2 between surgical and ineligible surgical groups (p <0.05).

Table 3. Circulatory characteristics of the patients when hospital admissions

	Surgery (n=125)	Ineligible surgery (n=35)	p-value
Heart rate (bpm) (mean ± SD)	138± 19	150 ± 21	< 0.01
MBP (mmHg) (mean± SD)	45 ± 11	40± 10	< 0.05
Lactate (mg/l) median (min-max)	1.9 (0.5-15.0)	5.0 (0.6-15.0)	< 0.001

Higher heart rate, lower blood pressure, and higher lactate were statistically significant differences between surgical and ineligible surgical groups.

Table 4. Pulmonary artery pressure and pulmonary hypertension when admissions

		Surgery (n=125)	Ineligible surgery (n=35)	p-value
PAP (mmHg, mean±SD)		41 ± 19	64± 12	< 0.001
PAH (n,%)				
	No PAH	40 (33.3)	1 (2.9)	
	Mild PAH	19 (15.8)	0 (0)	< 0.001
	Medium PAH	51 (42.5)	17 (50.0)	
	Severe PAH	10 (8.3)	16 (47.1)	

The difference on the PAP between surgical and ineligible surgical groups was statistically significant (p<0.05). In particular, there were more patients in ineligible surgery group suffered severe PAH compared to surgery group.

Table 5. Investigators laboratory among the patients

	Surgery (n=125) (Mean ± SD)	Ineligible surgery (n=35) (Mean ± SD)	p-value
Hemoglobin (g/dl)	14.70 ± 1.95	14.35± 2.56	> 0.05
Thrombocyte (G/l)	218.4 ± 74.1	176.6± 66.7	< 0.01
Prothrombin (%)	57.8 ± 15.6	43.3± 15.9	< 0.001
aPTT (s)	40.6 ± 8.8	53.2± 23.2	< 0.001
pH	7.31 ± 0.14	7.11± 0.18	< 0.001
glucosemia (mmol/l)	5.07± 1.58	6.35± 4.90	< 0.05
Albumin (g/l)	33.2 ± 3.9	31.3 ± 4.7	< 0.05
Ure (mmol/l)	4.05 ± 1.65	5.19 ± 2.86	< 0.01
Creatinine (mcmol/l)	73.9 ± 23.9	98.4 ± 31.3	< 0.001

There were statistically significant differences in coagulation disorders (lower platelet, low rate of lower prothrombin, and prolonged aPTT), lower blood pH, lower blood albumin, higher ure, and higher creatinine between surgical and ineligible surgical groups (p <0.05).

Table 6. Multivariate analysis of risk factors for ineligible surgery's group

Risk factors	OR	95% CI
Hypothermia < 36^0 C	7.18	1.56 – 33.13
PaCO2 > 60 mmHg	9.66	2.73 – 34.19
Lactat > 2.5 mg/L	7.21	2.11 – 24.60
PAP > 55 mmHg	15.36	3.80 – 62.10
Thrombocytes < 150 000 G/L	7.69	1.93 – 30.54

The risk factors for ineligible surgery of CDH patients were hypothermia below 36 degrees C; PaCO2 over 60 mmHg; Lactate over 2.5 mg / L; and pulmonary artery pressure above 55 mmHg; and platelets below 150,000 G / L.

4. DISCUSSIONS

The congenital diaphragmatic hernia was described many years ago. The herniation of abdominal into the thorax in the fetus due to the lungs were hypoplastic and had abnormal vessels that cause respiratory insufficiency and persistent pulmonary hypertension. Thus, respiratory and cardiovascular functions are severely compromised at birth. These health conditions, together with the frequently associated malformation, cause considerable mortality and morbidity [1,4,11,12].

There were 160 patients taking part in this study. Of which, 35 patients did not meet the criteria for surgery, ineligible surgery and died afterward (21.9%). This rate is similar to some studies. Lally et al showed that this rate was 18% when collecting data in 3,062 CDH patients at 51 centers in 8 countries [7]. Pei-Hsin Chao and his colleagues indicated that the mortality rate in 24 CDH patients was 21%, and most of them had died before surgery [8]. A cohort study (1994-2005) in 111 patients conducted by Migliazza and his colleagues showed that the percentage of the patients who did not meet operative criteria was 10.8% [9].

The epidemiological, clinical and investigators laboratory in both surgical and ineligible surgical patients when hospital admissions (Tables 1, 2, 3, 4, 5) indicated severe conditions that required to have respiratory, cardiovascular, and homeostasis resuscitation. The patients should be fully resuscitated, including hypothermia, the respiratory distress with oxygen insufficiency low PaO2/FiO2 ratio and high PaCO2 concentration, low blood pressure, high lactate, treatment of pulmonary arterial hypertension, and other problems related resuscitation as coagulation disorders and kidney failure.

The mortality rate of CDH remains high in spite of many surgical advances. Respiratory failure and pulmonary artery pressure are major barriers for resuscitating these patients. A recent method of preoperative resuscitation that enables to decrease the mortality rate is delaying surgery until several indexes and health status being stable. The surgery might be delayed for several days or weeks until the condition of pulmonary artery pressure is improved [7,11].

As recommended in the CDH EURO Consortium 2010, it includes postpartum tracheal intubation, gentle ventilation, control pulmonary hypertension, and delayed surgery for stable conditions. Specific tasks in the

neonatal ICU are based on the strategy of gentle ventilation to achieve pre-ductal saturation above 85-95%, pH above 7.20, and lactate 3-5 mmol/l; conventional mechanical ventilation with a maximal PIP of 25-28 cmH2O or a HFO with maximal MAP of 17 cmH2O, normalized blood pressure at gestational ages, and consideration of vasopressors. An appropriate treatment of pulmonary hypertension requiring bedside Doppler echocardiography, indicate iNO if available, if there is no response, it is necessary to stop using iNO. Extracorporeal membrane oxygenation (ECMO) will be indicated for the treatment if some index is not maintained, including unable keep pre-ductal saturation 85%, respiratory acidosis, inadequate oxygen delivery (lactate > 5 mmol/l). This Consortium suggested the timing surgical repair suitable when FiO2 below 0.5, mean blood pressure normal for gestational age, urine output above 2 ml/kg/h and no signs of PAH [11,12].

In this study, risk factors for ineligible surgical patients, died afterward (Table 6) were hypothermia below 36°C; PaCO2 over 60 mmHg; lactate over 2.5 mg/L; pulmonary artery pressure over 55 mmHg; and platelets under 150,000 G/L.

Choosing the best solution for hypercapnia is gentle ventilation, such as avoidance of high pressures (peak pressure 25 cmH2O and peak and-expiratory pressure, 5 cmH2O and accepting higher levels of PaCO2 (permissive hypercapnia up to 60-65 mmHg). Pediatric intensivist aimed to minimize lung injury by limiting the peak airway pressure and allowing permissive hypercapnia, rather than aiming for low PaCO2 to reduce pulmonary vascular resistance. HFO and ECMO are using in many CDH's centers for alternative forms of support, the results will be very welcome to inform the choice of respiratory support [6,10,11]. In this population, we are lack of resources for using ECMO because it is very expensive in Viet Nam.

The severity of pulmonary hypertension predicts the outcome, nonsurvivors in our study. Some studies showed that iNO improves oxygenation in up to 50% of cases, but the effect may be transitory and use of iNO does not influence overall outcome. Sildenafil, a phosphodiesterase type 5 inhibitor, has been used to improve oxygenation and cardiac output by reducing pulmonary hypertension refractory to iNO. It may also prevent rebound pulmonary hypertension during weaning iNO [12].

Hypercapnia and pulmonary hypertension are truly risk factors that are barriers to performing the surgical repair in our CDH population. They are also known as prognostic factors for died cases.

To date, some postnatal majors clinical prediction rules have been published. These models contain variables such as birth weight, Apgar score, blood gases, as well as a measure of pulmonary hypertension, and associated abnormalities. The appropriate selection and application of CDH prediction rules provide an opportunity for benchmarking, standardizing strategies, and centralizing the care of high-risk population [13,14].

5. CONCLUSIONS

The rate of preoperative mortality among CDH patients in the Vietnam National Children's Hospital, who were unable to receive surgery, was 21.9%. The preoperative risk factors that prevented the CDH patients from receiving surgery were the temperature < 36°C, $PaCO_2$ >60mmHg, pulmonary hypertension > 55 mmHg, and platelets < 150,000 G/L.

REFERENCE

1. Lally KP. (2005). Congenital diaphragmatic hernia. In: Principles and Practice of Pediatric Surgery. vol. 4. Philadelphia: Lippincott Williams & Wilkins; 898-908.

2. Logan JW, Rice HE, Goldberg RN, et al (2007). Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. Journal of perinatology: official journal of the California Perinatal Association, 27(9): 535-549.

3. Wynn J, Krishnan U, Aspelund G, et al (2013). Outcomes of congenital diaphragmatic hernia in the modern era of management. The Journal of pediatrics 163(1):114-119 e111.

4. Mielniczuk M, Kusza K, Brzezinski P, et al (2012). Current management of congenital diaphragmatic hernia. Anaesthesiology intensive therapy , 44(4):232-237.

5. Nguyen Thanh Liem, Lo Quang Nhat, To Manh Tuan et al. (2011). Thoracoscopic repair for congenital diaphragmatic hernia: Experience with 139 cases. J. Laparoendosc Adv Surg Tech A; 21(3): 267-270.

6. Nguyen Thanh Liem, Tran Minh Dien, Nguyen Quang Ung (2010). Thoracoscopic Repair in the Neonatal Intensive Care Unit for Congenital Diaphragmatic Hernia During High-Frequency Oscillatory Ventilation. J Laparoendosc Adv Surg Tech A, 20(1): 111-114.

7. Chao PH, Huang CB, Liu CA, Chung MY, et al. (2010). Congenital diaphragmatic hernia in the neonatal period: review of 21 years' experience. Pediatrics and neonatology, 51(2):97-102.

8. Lally K. P., Lally P. A., Lasky R. E., et al (2007). Defect size determines survival in infants with congenital diaphragmatic hernia. Pediatrics, 120(3):e651-657.

9. Migliazza L, Bellan C, Alberti D, et al (2007). Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. Journal of pediatric surgery, 42(9): 1526-1532.

10. Datin-Dorriere V., Walter-Nicolet E., Rousseau V., et al (2008). Experience in the management of eighty-two newborns with congenital diaphragmatic hernia treated with high-frequency oscillatory ventilation and delayed surgery without the use of extracorporeal membrane oxygenation. Journal of intensive care medicine, 23(2):128-135.

11. Kotecha S, Barbato A, Bush A. (2012). Congenital diaphragmatic hernia. The European respiratory journal , 39(4):820-829.

12. Reiss I., Schaible T., van de Hout L. et al (2010). Standardized postnatal management of infant with congenital diaphragmatic hernia in Europ: the CDH EURO consortium consensus. Neonatalogy; 98(4): 354-364.

13. Baird R., MacNab Y.C., Skarsgard E.D., et al (2008). Mortality prediction in congenital diaphragmatic hernia. Journal of Pediatric Surgery; 43(5): 783-787.

14. Daodu O., Brindle M.E., (2017). Predicting outcome in congenital diaphragmatic hernia. Seminar in Pediatric Surgery; 26: 136-139.