Early outcome of congenital diaphragmatic hernia in a Malaysian tertiary centre

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ABSTRACT

Introduction: This prospective observational study was conducted to determine the outcome of newborns with congenital diaphragmatic hernia (CDH). They were managed with a protocol of gentle ventilation to avoid barotraumas, and inhaled nitric oxide (iNO) or intravenous magnesium sulphate for treatment of persistent pulmonary hypertension of newborns (PPHN).

Methods: All newborns with CDH admitted to neonatal intensive care unit of this hospital during the six-year study period were recruited. High frequency oscillatory ventilation was used when infants required peak inspiratory pressure of more than 25 mmHg. iNO at 20 ppm or intravenous magnesium sulphate was used when PPHN developed. Arterial blood pH was maintained between 7.35 and 7.45, and partial pressure of arterial carbon dioxide was kept above 35 mmHg. Surgery was performed when the infants' general condition and blood gases were stabilised for at least 24 hours.

Results: Of 21 infants recruited (15 males and six females, median gestational age 39.0 weeks, median birth weight 2,800 grams), 52.4 percent had PPHN. 12 (57.1 percent) underwent surgery at a median age of 4.9 days. One died postoperatively due to PPHN. Out of the 21 subjects, 11 (52.4 percent) survived to discharge. There was no significant difference in the demographic characteristics, side and size of CDH defects, presence of PPHN, or type of treatment received, between infants who survived and died. However, infants who died had significantly lower mean Apgar scores at five minutes of life (p-value is 0.02), and higher mean oxygenation indexes (OI) (p-value is 0.01) than those of survivors. Two (18.2 percent) of the II survivors developed chronic lung disease.

<u>Conclusion</u>: Low Apgar scores and high OI were associated with poor outcome in infants with CDH. Keywords: congenital diaphragmatic hernia, inhaled nitric oxide, magnesium sulphate, persistent pulmonary hypertension of newborns Singapore Med | 2008;49(2): 142-144

INTRODUCTION

Congenital diaphragmatic hernia (CDH), although rare (1 per 2,000-4,000 births), is associated with high mortality (36% based on the CDH registry).⁽¹⁾ Specialised centres with extracorporeal membrane oxygenation (ECMO) facilities reported survival rates of almost 80%.^(2,3) Current management strategies consists of preoperative stabilisation and delayed repair.⁽⁴⁾ ECMO facilities are not available in most Asian countries. Various other treatment strategies were developed by different centres to improve outcome. High frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) were first made available at our centre in the late 1990s. Prior to this, newborns with CDH were ventilated using conventional ventilators and intravenous magnesium sulphate (MgSO₄) for treatment of persistent pulmonary hypertension of newborns (PPHN). A protocol, which focused on gentle ventilation and treatment of PPHN with iNO or MgSO4 was developed in our centre. This study was conducted to determine the early outcome of newborns with CDH treated according to this protocol.

METHODS

This was a prospective, observational study conducted at the neonatal intensive care unit (NICU) of Hospital Universiti Kebangsaan Malaysia. This hospital is a tertiary referral centre with neonatal surgery services. All newborns with CDH admitted over a six-year period (between January 1, 2000 and December 31, 2005) were treated according to a standard protocol. HFOV was used when infants required a peak inspiratory pressure (PIP) of more than 25 mmHg on conventional ventilators. iNO at 20 ppm, or intravenous MgSO4, was commenced when PPHN, confirmed by echocardiography, developed. Intravenous MgSO₄ was used as the first-line vasodilator only if the infants' blood pressure was normal. Infants treated with intravenous MgSO4 were given a loading dose of MgSO4 at 200 mg/kg infused over half an hour, followed by a continuous infusion of maintenance dose of MgSO₄ at 25-50 mg/kg/hour to achieve a serum level of magnesium of 5.0-7.0 mmol/L. The serum level was checked and measured every 12 hours. Patients were

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Correspondence to: Dr Rohana Jaafar Tel: (60) 3 9170 2049 Fax: (60) 3 9173 7827 Email: drohana@ mail.hukm.ukm.my switched to the second vasodilator (iNO or MgSO₄) whenever their condition deteriorated or PPHN persisted after four hours of treatment with the first vasodilator. The first vasodilator was weaned off over 12–48 hours depending on the response of infants. Arterial blood pH was maintained between 7.35 and 7.45, and a partial pressure of arterial carbon dioxide (PaCO₂) was kept at between 35 and 50 mmHg. Surgery was performed when infants' vital signs, general condition, and blood gases were stabilised for at least 24 hours.

The oxygenation index (OI), a measure of the level of ventilatory support and the severity of hypoxaemia of the infants, was serially monitored. It was calculated from the following equation:

 $\frac{[Mean airway pressure \times fraction of inspired oxygen (FiO_2) \times 100]}{postductal PaO_2,}$

where postductal PaO2 was expressed in mmHg.

The data was collected prospectively and analysed using the Statistical Package for Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA). Chi-square test was used to compare categorical variables. Independent *t*-test was used for analysis of normally distributed continuous data, while Mann-Whitney U test was used for analysis of skewed data. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

21 infants were treated (15 males and six females) during the study period. The median gestational age and birth weight were 39.0 (interquartile range [IQR] 4.0) weeks and 2,800 (IQR 675) grams, respectively. A majority (61.9%) of infants were inborn. CDH was prenatally diagnosed in 28.6% of infants. The lesions were left-sided in 15 (71.4%), and isolated (without other congenital anomaly) in 16 (76.2%) of the infants. Extensive shift of mediastinum was seen in the chest radiographs of 14 (66.7%) infants. 15 (71.4%) infants were ventilated using HFOV. PPHN occurred in 11 (52.4%) infants. Nine infants died before surgery could be carried out. 12 (57.1%) underwent surgery at a median age of 4.9 (IQR 3.6) days. The median OI prior to surgery was 5.8 (IQR 18.5). Surgery was performed on two infants in the NICU while on HFOV and iNO therapy, because they were too unstable for transfer to the operation theatre. One infant died postoperatively due to PPHN. 11 (52.4%) infants, out of the total number of study subjects, survived to discharge with a median hospital stay of 36 (IQR 25) days. Two (18.2%) survivors developed chronic lung disease.

There was no significant difference in the ethnic and gender distributions between infants who survived or died (Table I). Neither were there any differences in gestational age, birth weight, places of birth, prenatal diagnosis, and modes of delivery between the two groups. However, infants who had significantly lower mean Apgar scores at 5 minutes of life (p = 0.02). There was no significant

difference in the side of CDH, presence of extensive mediastinal shift or associated abnormality between the two groups (Table II). A higher proportion of infants who developed PPHN died, but this was not statistically significant. Infants who died, however, had significantly higher OI, reflecting more severe PPHN than the survivors (p = 0.04).

DISCUSSION

In recent years, various therapeutic modalities have been used to improve the outcome of infants with CDH. However, it remains unclear which strategy or combination of strategies offers the best survival rates. Most of the reported studies were non-randomised and the number of patients was small. From the limited evidence available, better outcomes were reported in infants delivered at tertiary centres, with surgical repair delayed until haemodynamic and respiratory stability were achieved, and with the judicious use of non-aggressive mechanical ventilation and permissive hypercapnia. Other therapeutic modalities, such as HFOV, iNO, and ECMO, may provide additional advantages for selected infants.⁽⁴⁾ Our study showed that the condition of more than 50% (n = 12) of infants with CDH when treated with combinations of gentle ventilation and treatment of PPHN with iNO or MgSO4, could be stabilised to undergo surgery. 91.7% (11/12) of them survived to discharge. The major weakness of the present study, however, lies in it being a non-randomised controlled trial. Furthermore, the number of infants recruited was small.

The overall survival rate from our series of patients was 52.4%. The CDH registry reported a survival rate of 64%,⁽¹⁾while a centre in Australia, which used ECMO, had a higher survival rate of 78%.⁽⁵⁾ The infants who died in our study had a median highest OI of 48.4. OI of greater than 40 predicts a high mortality and has been widely used as criteria for ECMO.⁽⁶⁾ A centre in Italy, which followed a similar protocol to ours, except for administration of surfactant when persistently high levels of FiO2 were needed to maintain PaO₂ values > 60 mmHg, reported the a higher survival rate of 60%.⁽⁷⁾ The CDH Study Group compared 192 surfactant-treated with 330 non-surfactant treated infants (non-randomised) and concluded that no benefit was associated with surfactant therapy.⁽⁸⁾ Large prospective controlled trials are required for confirmation of its beneficial role.

Since the 1980s, delayed surgery has become a widely accepted strategy for treatment of CDH and after Sakai et al reported the worsening of cardiopulmonary function following early surgical repair.⁽⁹⁾ Delayed surgery allows for stabilisation of newborns with CDH associated with lung hypoplasia and PPHN. The optimal timing of surgery is still not universally accepted. The mean age at repair varied between 4.5 and 8.9 days.^(2,10) Rozmiarek et al reported that cardiac defects, renal failure and initial blood gases were significant factors that influenced survival and not the timing of surgery.⁽¹¹⁾ Therefore, the timing

| Perinatal variables | Died n = 10 | Survived n = 11 | p-value |
|-----------------------------------|----------------|--------------------|---------|
| | | | |
| Malay (%) | 8 (80) | 8 (72.7) | 0.5 |
| Inborn (%) | 8 (80) | 5 (45.5) | 0.2 |
| Prenatal diagnosis (%) | 3 (30) | 3 (27.3) | 1.0 |
| Modes of delivery | | | |
| Spontaneous vertex delivery | 6 | 8 | 0.06 |
| Vacuum | 0 | 2 | |
| Forceps | 4 | 0 | |
| Lower segment Caesarean section | 0 | I | |
| Mean gestation (SD) (weeks) | 39.3 (2.7) | 37.8 (2.2) | 0.2 |
| Median birth weight (IQR) (g) | 2,840 (915) | 2,800 (750) | 0.9 |
| Mean Apgar score at one min (SD) | 5.2 (2.4) | 7.2 (1.5) | 0.05 |
| Mean Apgar score at five min (SD) | 6.9 (1.8) | 8.7(1.2) | 0.02* |

Table I. Comparison of demographical and perinatal variables between infants who died and survived.

* statistical significance.

Table II. Comparison of characteristics of diaphragmatic hernia and clinical variables between infants who died and survived.

| Clinical variables | Died n = 10 | Survived n = 11 | p-value |
|--|----------------|--------------------|---------|
| | | | |
| Left | 8 (80) | 7 (63.6) | |
| Right | 2 (20) | 4 (36.4) | 0.06 |
| Presence of extensive mediastinal shift (%) | 8 (80) | 6 (54.5) | 0.40 |
| No associated abnormality (isolated CDH) (%) | 8 (80) | 8 (72.7) | 1.00 |
| Developed PPHN (%) | 7 (70) | 4 (36.4) | 0.08 |
| Ventilated with HFOV (%) | 9 (90) | 6 (54.5) | 0.20 |
| Median highest oxygenation index (IQR) | 48.4 (87.5) | 22.9 (31.6) | 0.004* |

CDH: congenital diaphragmatic hernia; PPHN: persistent pulmonary hypertension; HFOV: high frequency oscillation ventilation; IQR: interquartile range

* statistical significance

of surgery should be based on optimising these clinical parameters, as opposed to adhering to a specific time period. This is reflected in our series, in which the age at surgery was highly variable, with a mean and median age of 5.6 (SD 3.6) and 4.9 (IQR 3.6) days, respectively.

iNO for CDH has been associated with good outcome in some centres, but other groups reported disappointing results.⁽⁷⁾ Three of our patients with PPHN received only iNO as a vasodilator and all of them died. One newborn who received only MgSO4 also died. Two newborns who received MgSO4 as the first vasodilator survived, while another two who received iNO as the first vasodilator died. This suggests that MgSO4 may be effective but takes a longer time to take effect. However, this needs to be confirmed by a proper randomised trial. Three other patients with PPHN were not given vasodilator because they had associated lethal cardiac malformations. In conclusion, this small observational study showed that low Apgar scores and high initial OI were associated with poor early outcome of CDH. There is a need to do properly-controlled studies involving a good number of infants with CDH to answer some of the critical questions about the management and outcome of these infants.

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