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Congenital diaphragmatic hernia; 10-year evaluation of survival, ECMO and FETO in 4 high-volume centres

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Short title: Congenital diaphragmatic hernia; survival, ECMO & FETO

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ABSTRACT

Background: Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with significant mortality.

Objectives: To determine if there were trends in survival over the last decade and to compare patient populations, treatment options and survival rates between four high-volume centres and hence determine which factors were associated with survival.

Methods: In four high-volume CDH centres from the CDH EURO Consortium, data from all CDH patients born between 2004- 2013 were analysed. The predictive value of variables known at birth and the influence of centre-specific treatments (extracorporeal membrane oxygenation (ECMO) and fetoscopic tracheal occlusion (FETO)) on survival were evaluated in multivariable logistic regression analyses.

Results: Nine hundred and seventy-five patients were included in the analysis; 274 patients (28.1%) died. ECMO was performed in 259 patients of whom 81 (31.3%) died. One hundred and forty-five patients (14.9%) underwent FETO and from those 76 patients (52.4%) survived. Survival differed significantly between years ($p=0.006$) and between the four centres ($p<0.001$). In the multivariable logistic regression analysis, lung-to-head ratio, gestational age at birth, ECMO, centre of birth, and year of birth were significantly associated with survival, whereas FETO was not.

Conclusions: Patient populations were different between centres which influenced outcome. There was a significant variability in survival over time and between centres which should be taken into consideration in the planning of future trials.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly with a high variability of outcome [1]. Over the last decade new strategies have been introduced to evaluate and manage CDH patients. It is likely then that survival may have improved over that time, an aim of our study was to test that hypothesis.

Patient characteristics such as fetal liver position (intra-abdominal or intrathoracic) [2], stomach position [3], and lung-to-head ratio (LHR) [4]/ observed-to expected LHR [5] and the diaphragmatic defect size [6] can influence outcome as well as treatment in a high or low volume centre. There are differences in opinion about whether extracorporeal membrane oxygenation (ECMO) improves survival as no specific trials have been conducted with the primary aim of evaluating the role of ECMO specifically for high-risk CDH patients [7, 8]. The UK ECMO randomised trial investigated the role of ECMO for neonates, but only 19% of those included had CDH and there was no significant difference in that subgroup with regard to survival [9]. In a multicentre, randomised, clinical trial (RCT) of initial ventilation strategy, in which centres with and without ECMO availability were included, no difference in survival between centres was observed [10]. Many CDH centres chose not to use ECMO because of the perceived poor outcome of CDH infants requiring ECMO [11]. Therefore, an important question is does ECMO influence survival? In the most severe, prenatally detected CDH cases, fetoscopic endotracheal occlusion (FETO) may improve outcome [12, 13]. To date, however, the results of only one small RCT have been reported. In an RCT of 20 severe CDH patients of FETO versus postnatal management, survival was significantly better in the FETO group [14]. Thus, it is important to further determine the influence of FETO on survival while the results of the so called TOTAL trial are to be available in 2018. Analysing the results of four high-volume CDH centres our further aim, therefore, was to compare patient populations, treatment options and survival rates to determine which factors were associated with survival.

PATIENTS AND METHODS

An observational cohort study was performed of all patients with CDH who were born between January 2004 and December 2013 and treated in four high-volume centres of the CDH EURO Consortium. The four centres were Rotterdam, London, Mannheim and Rome. Since 2008, all patients have been treated according to a standardized treatment protocol [15]. The standardized treatment included immediate intubation after birth, permissive hypercapnia, initial ventilation by high-frequency oscillation or

conventional mechanical ventilation, surgical repair of the defect after physiological stabilization, no routine chest tube placement, no routine use of paralysis. ECMO was only used routinely in some centres. In Rotterdam and Mannheim, ECMO therapy was available during the whole inclusion period, in Rome ECMO was available in 2013 only and in London infants could be transferred to an ECMO centre. FETO was available in the four centres on compassionate use.

ECMO criteria were an inability to maintain preductal saturations >85% or postductal saturations >70%; a high $PaCO_2$ with a respiratory acidosis (pH <7.15) despite optimization of ventilatory management (peak inspiratory pressure >28 cm H_2O or mean airway pressure >17 cm H_2O to achieve saturation >85%; inadequate oxygen delivery with a metabolic acidosis, lactate level >5 mmol/l and pH <7.15); systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output <0.5 ml/kg/h for at least 12–24 hours; oxygenation index (mean airway pressure x FiO_2 x 100/PaO_2) ≥40. Before 2008, in Mannheim, ECMO criteria included an oxygenation index >35 for 0.5- 6 hours and a pH <7.25. In London, FETO therapy was only offered within the context of research trials (NCT01240057) from 2013 onwards and before 2010 as compassionate use. Inclusion criteria for FETO were: isolated left-sided CDH and severe pulmonary hypoplasia defined as observed-to-expected LHR <25% as measured prior to 29 weeks+ 6 days, irrespective of the liver position.

Patient demographics and management strategies, including prenatal diagnosis, LHR, FETO, gestational age, birth weight, gender, side of the defect, liver position (intrathoracic or intra-abdominal determined during surgical repair), type of repair (primary closure or patch repair), age at surgical repair, ECMO, ventilation days in survivors, inhaled nitric oxide (iNO) and survival were collected from the medical records. Death during the first year after birth was determined.

Analysis

To determine whether differences in the demographics of the infants in the four centres were statistically significant, chi-square tests for categorical data, or Kruskal-Wallis tests for continuous data were used. Mann-Whitney U tests for continuous data and chi-square tests for categorical data were applied to compare centre of birth and patient characteristics that were known at birth between survivors and non-survivors. In these univariate comparisons, year of birth was treated as a categorical variable. Associations between prenatal diagnosis, LHR, FETO, gestational age, gender, side of the defect, ECMO, centre and year of birth as independent variables and survival were determined using multivariable logistic regression analysis. The goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow test. Analyses were performed using SPSS 22.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

During the study period, there were 975 CDH patients; 274 (28.1%) patients died. A prenatal diagnosis was made in 820 (84.1%) patients. Overall, there was a significant difference in survival over the years (p=0.006) (Figure 1). The survival rate differed from 29% to 97% over the years and centres.

Prenatal diagnosis, LHR, FETO, gestational age, birth weight, gender, liver position at surgical repair, type of repair, age at surgical repair, ECMO, ventilation days in survivors, use of iNO and survival were significantly different between the four centres (Table 1). Survivors significantly less often had a prenatal diagnosis, had higher LHRs and gestational ages and a greater proportion had a left-sided defect than non-survivors (Table 2).

There were also significant differences in survival regarding year of birth and centre of birth (Table 2). In Mannheim, 196 patients (41.8%) received ECMO and 153 (78.1%) of the ECMO-treated patients survived. In Rotterdam, 62 patients (31.8%) received ECMO and 25 (40.3%) of the ECMO-treated patients survived. ECMO treated patients in Rotterdam had lower LHRs and more often had a patch repair compared to the ECMO treated patients in Mannheim. In Rome, in 2013 one patient received ECMO and died. None of the patients from London received ECMO. ECMO use between survivors and non-survivors was not statistically significant. FETO was significantly more often used in non-survivors (25.2%) than in patients who survived (12.5%).

In the multivariable logistic regression analysis, a lower LHR, lower gestational age, ECMO, centre of birth and year of birth were significantly associated with death (Table 3). FETO was not significantly associated with death. The p-value of the Hosmer-Lemeshow test was larger than 0.05, indicating an adequate model calibration.

DISCUSSION

We have demonstrated variability in survival across a ten year period and between four high volume CDH centres. In addition, we highlight that the patient populations differed significantly between the centres and this influenced outcome. The survival rate was very different each year (Figure 1).

In the univariable analysis, we did not find a significant difference in ECMO use between survivors and non-survivors. In the multivariable analysis with correction for patient characteristics, however, we found that ECMO was significantly associated with death. This may be explained by the fact that only the most severe CDH cases receive ECMO. The frequency of use of ECMO and the outcomes was different between centres. In Mannheim 42% of the patients received ECMO and 78% of them survived, whereas in Rotterdam 32% of the patients received ECMO and only 41% of them survived. ECMO treated patients in Rotterdam, however, had lower LHRs and more often had a patch repair, suggesting they were in a more severe category. To identify for which subgroup of CDH patients ECMO might be most beneficial, predictive postnatal clinical models such as the Score for Neonatal Acute Physiology-II [16] or the clinical prediction score by Brindle et al [17] may be useful.

FETO was significantly more often used in non-survivors likely reflecting the selection criteria for compassionate use. Because FETO was only used on a compassionate basis, it precludes any meaningful conclusion with regards to the influence of FETO on survival. Hopefully, the TOTAL trial [18] will give a definitive answer to the benefit of FETO for patients with severe CDH.

High-volume CDH centres have more experience in treating CDH infants than low-volume centres and better outcomes [19]. Nevertheless, the patient characteristics were very different between the four high-volume centres and, despite correction for patient characteristics in the multivariable analysis, centre significantly influenced survival. This emphasizes the need for correction for centre in analyses of future multicentre studies on CDH.

Our study has many strengths and some limitations. We examined the outcome of a large sample (n=975) over ten years in four high-volume centres. Despite all centres during the study period had agreed use of a consistent protocol, we cannot rule out the possibility that differences in physicians, nursing staff and training may have influenced our results. This needs to be taken into account in future RCTs.

CONCLUSION

We have demonstrated variability in survival of CDH patients over time and between centres. Such differences need to be taken into account when planning future trials.

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Figure 1. Survival of CDH by centre over the years

Figure 1