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ORIGINAL ARTICLE

Reduction in ventilator-induced lung injury improves outcome in congenital diaphragmatic hernia?

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Abstract The purpose of this historical study was to compare the outcome for two treatment strategies, for neonates with congenital diaphragmatic hernia (CDH). The records of 65 infants born between 1991 and 2005 with CDH from a single tertiary care perinatal centre in the United Kingdom were retrospectively reviewed. Conventional mechanical ventilation (CMV) and systemic vasodilators were used from 1991 to 1995 (era 1). High frequency oscillatory ventilation (HFOV) and nitric oxide (NO) were used between 1996 and 2005 (era 2). Main outcome measures were survival and incidence of chronic lung disease. The results showed that the survival rate was 38% (8/21) in era 1 and 73% (32/44) in era 2, 95% CI for difference −59 to −10%. The incidence of chronic lung disease in survivors was 45% (5/11) in era 1 and 30% (9/30) in era 2, 95% CI for difference −18 to 49%. These data show significantly improved survival with elective use of HFOV and NO compared to CMV and systemic vasodilators. The survival results for CDH at St George's Hospital are comparable to those published from other institutions. The results may reflect a reduction in ventilator-induced lung injury with HFOV compared to CMV.

Keywords Congenital diaphragmatic hernia · Outcome

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Introduction

The incidence of congenital diaphragmatic hernia (CDH) has been reported as 0.17–0.66 per 1,000 births [1]. Approximately 80% of all CDHs occur in the left hemithorax and up to 50% of cases are associated with the presence of other abnormalities [2]. Despite the advances in neonatal intensive care the condition is associated with a high mortality and morbidity due to the presence of pulmonary hypoplasia, pulmonary hypertension, chromosomal defects and associated malformations. The anatomical defect is of secondary importance to the main underlying pathophysiology consisting of a combination of lung hypoplasia and persistent pulmonary hypertension secondary to a reduction in the number of arterial branches and medial thickening of the small preacinar and intraacinar arterioles. Management of infants with CDH includes therapy directed towards the treatment of both these factors.

Repair of the hernia is no longer considered a surgical emergency. Delayed repair allows time for pulmonary hypertension to resolve [3] and has been associated with improved survival [4–6]. Over the last 10 years newer strategies for the management of persistent pulmonary hypertension of the newborn (PPHN) have emerged. These include high frequency oscillatory ventilation (HFOV),

permissive hypercapnia, nitric oxide (NO) and extra-corporeal membrane oxygenation (ECMO) although the role of these treatments in congenital diaphragmatic hernia remains controversial. Some centres advocate using early HFOV [7, 8] as the lower alveolar pressure and volume variations should theoretically reduce barotrauma and volutrauma. In addition animal work has demonstrated HFOV results in more uniform lung inflation [9] and this may be advantageous in hypoplastic lungs. Reduction in pressure can also be achieved with permissive hypercapnia and this strategy was advocated by Wung et al. [10] in infants with persistent pulmonary hypertension of the newborn. Limitation of airway pressure and tolerance of hypercarbia may be important factors influencing outcome in congenital diaphragmatic hernia [11].

Nitric oxide (NO) may be used with either HFOV or CMV. Nitric oxide regulates vascular smooth muscle tone and acts as a selective pulmonary vasodilator. It is now widely used for the treatment of persistent pulmonary hypertension and a study by Kinsella et al. [12] suggested that nitric oxide and HFOV were more beneficial than either treatment alone. However, the NINOS trial did not demonstrate a beneficial effect of NO in infants with CDH [13] although this trial was limited by the small number of infants. The use of ECMO for the treatment of congenital diaphragmatic hernia is also controversial. Large studies in North America report a survival rate between 66 and 79% to discharge from hospital using ECMO and delayed repair [14–16]. However the UK ECMO Trial [17] demonstrated no benefit from ECMO over conventional management in the treatment of congenital diaphragmatic hernia although the number of infants in this study was small.

Despite these new strategies for the management of neonates with congenital diaphragmatic hernia, the outcome remains poor. In 1996, we changed our postnatal management of these infants from conventional ventilation and systemic vasodilators to HFOV and nitric oxide. The purpose of this study was to evaluate the influence of this change in strategy on outcome.

Materials and methods

The neonatal unit at St George's Hospital (SGH), London is a tertiary centre admitting inborn and outborn neonates with both medical and surgical problems. Robust data for infants with CDH were available from 1991 and between 1991 and 2005, 65 newborn infants with CDH were admitted to the unit and these infants are the subjects of this historical study. Throughout both therapeutic eras, the delivery room management of all infants with an antenatal diagnosis of CDH and delivered at SGH remained the same and included endotracheal intubation, paralysis and elective ventilation at birth and passage of a nasogastric tube. However from 1996 postnatal management changed from conventional ventilation and systemic vasodilators to HFOV and NO.

Therapeutic era 1 (1991–1995)

This era included 21 infants admitted to our neonatal unit with a diagnosis of CDH. Infants requiring intubation preoperatively were ventilated with CMV and where necessary PPHN was treated with systemic prostacyclin. We aimed to keep the pCO_2 within the normal range and the arterial pO_2 between 9 and 10 kPa. Prostacyclin use was guided by pre and post ductal saturations and an inability to maintain an arterial pO_2 of 7 kPa despite optimal ventilation. Four infants who could not be stabilized with these treatment modalities were referred for ECMO. Operative treatment was undertaken only when the infant was off inotropes and ventilatory parameters were stable i.e. ventilatory pressures and oxygen requirements were not increasing.

Therapeutic era 2 (1996–2005)

During this period 44 infants were admitted with CDH. Infants with an antenatal diagnosis of CDH and delivered at SGH were treated with HFOV using a high volume strategy strategy i.e. MAP was increased until it was possible to wean F_iO_2. NO was used to reduce pulmonary vascular resistance if a FiO_2, ≥ 0.6 was required to maintain a paO_2 of ≥ 6.5. The diagnosis of pulmonary hypertension was made by echocardiography. Inborn infants diagnosed after birth or those transferred from another hospital who required ventilation were also treated with HFOV on admission and the same criteria were used for commencing NO. One infant who could not be stabilized with these treatment modalities was transferred for ECMO.

Information obtained retrospectively from records of all infants was entered into a database. Data on antenatal diagnosis, birth weight, sex, laterality of hernia, associated anomalies, survival, postnatal age at time of surgery, mode of ventilation and number of days requiring ventilation were collected. Mean airway pressure (MAP), fractional inspired oxygen concentration (FiO_2), pO_2 and pCO_2 at 0, 12, 24 h from birth and post operatively were also recorded as well as presence of chronic lung disease (CLD), defined as oxygen dependence at 28 days, and age at discharge from hospital. The primary outcome measure for each therapeutic era was mortality.

Continuous outcomes were compared with use of the Mann–Whitney *U* test. When numbers were small

categorical outcomes were compared using Fisher's exact test. The large sample Normal method was used to calculate 95% confidence intervals for differences where possible. A P value of <0.05 was taken as significant. All analyses were carried out using Stata v9 (StataCorp Stata Statistical Software: Release 9.0 College Station, Texas: Stata Corporation 2005).

Results

In the15-year period, 65 infants with CDH were admitted to St George's Hospital. As seen in Table 1, 50 infants (77%) were born at term (≥37 weeks). Birth weight ranged from 1,247 to 4,600 g (mean 3,038 g). The mean gestational age of preterm infants with CDH was 34.1 weeks (SD 1.5 weeks) and three of these infants received surfactant.

Eleven of the 65 infants (17%) had associated abnormalities: four in era 1 and seven in era 2. None of the abnormalities were lethal and no abnormality was thought to contribute to death. Abnormalities included syndactyly, Downs' syndrome, renal hypoplasia, cleft palate and cerebral atrophy. Six infants had cardiac anomalies (9.2%) including atrial septal defect, ventricular septal defect, pulmonary stenosis and coarctation of the aorta. A post mortem examination was performed in 21 of the 25 (84%) patients who died and no pathology other than pulmonary hypoplasia was confirmed as the cause of death.

The two groups were comparable in terms of demographics, initial oxygen index (Table 2) and FiO_2, pO_2 and pCO_2. Infants treated with HFOV and NO had a significantly higher survival rate (73 vs. 38%) ($P = 0.01$) and a lower incidence of chronic lung disease (30 vs. 45%) ($P = 0.36$) compared to those treated with conventional ventilation and systemic vasodilators. The mean number of days to operation was significantly greater in the second era (9.6 vs. 5.0, $P = 0.04$), but there was no significant difference in hospital stay between survivors or, for infants that died, age of death (Table 2). One infant in era 1 and two infants in era 2 were diagnosed after birth, not ventilated prior to operation and only required oxygen for respiratory support perioperatively.

Other factors that might predict survival, location of defect, gestational age and time of diagnosis, were also analysed. We did not record the size of the defect. Overall survival was significantly lower in infants who were born within the institution compared to those transferred to St George's after birth (19/24 vs. 21/41, $P = 0.03$) and higher in infants with defects diagnosed postnatally (20/25 vs. 20/40, $P = 0.02$). Right-sided CDH was not associated with greater mortality (8/16 vs. 17/49, $P = 0.28$), nor was having an additional defect (5/11 vs. 20/54, $P = 0.60$). Survival was higher for males than females (female, 12/28 vs. male, 28/37, $P = 0.01$) and was poorer if there was vasodilator requirement ($P = 0.01$). However, there was no significant difference in the incidence of any of these factors between the two eras (Table 1).

Discussion

The purpose of this historical study was to compare the outcome of CDH between two eras with different management strategies. In era 2, when HFOV and inhaled NO were used rather than CMV and systemic vasodilators the survival rate increased significantly from 38 to 73%. The use of early HFOV for infants with CDH has resulted in good survival rates in other centres [18] and our survival rate is similar to that found by Desfrere et al. [6]. This study also used HFOV on admission to the neonatal unit and surgery was delayed until the infant's ventilatory parameters were stable and the infant was off inotropes. The survival rates of other centres using HFOV in the management of CDH are variable and range from 55 to 86% [6, 7, 19–22]. Infants ventilated in era 2 also had a lower but non-significant incidence of chronic lung disease compared to those infants treated in era 1. We postulate

Table 1 Characteristics of infants

Characteristic	Era 1 [1991–1995]	Era 2 [1996–2005]	P value
Birth weight (g): mean [SD]	3,011 [584] $n = 21$	3,051 [686] $n = 44$	0.82
Gestational age [GA] (weeks): mean [SD]	38.0 [1.6] $n = 21$	37.7 [2.7] $n = 44$	0.62
GA < 37 weeks (no.) (%)	4/21 [19]	11/44 [25]	0.59
Male sex (no.) [%]	12/21 [57]	25/44 [57]	0.98
Born in institution (no.) [%]	11/21 [52]	30/44 [68]	0.22
Antenatal diagnosis (no.) [%]	10/21[48]	30/44 [68]	0.11
Left sided CDH (no.) [%]	15/21 [71]	34/44 [77]	0.61
Congenital abnormalities (no.) [%]	4/21 [19]	7/44 [16]	0.75
No. not requiring ventilation (no) [%]	1/21 [5]	2/44 [5]	1.00
No. requiring vasodilators	14/21 [67]	30/44 [68]	0.80

Table 2 Outcomes for both eras

	Era 1	Era 2	*P* value
Survival [%]	8/21 [38]	32/44 [73]	0.01
CLD those alive at 28 days [%]	5/11 [45]	9/30 [30]	0.36
Age of death (days): mean [SD]	29.5 [40.2] $n = 13$	21.0 [36.6] $n = 12$	0.45
Ventilation time (days): mean [SD]	18.7 [25.1] $n = 20$	14.2 [20.4] $n = 44$	0.45
Survivors ventilation time (days): mean [SD]	11.4 [8.9] $n = 8$	11.6 [8.9] $n = 32$	0.95
OI time 0: mean [SD]	25.8 [27.2] $n = 16$	26.2 [16.6] $n = 29$	0.41
OI time 12: mean [SD]	31.4 [33.9] $n = 18$	18.4 [24.3] $n = 32$	0.69
OI time 24: mean [SD]	14.3 [21.2] $n = 14$	16.4 [28.8] $n = 33$	0.36
OI post operative: mean [SD]	5.1 [5.8] $n = 10$	5.4 [4.0] $n = 30$	0.63
Time to surgery: mean [SD]	5.0 [3.9] $n = 13$	9.6 [11.5] $n = 33$	0.04
Length of stay of survivors at St George's Hospital (days): mean [SD]	25.2 [16.1] $n = 6$	35.8 [44.8] $n = 26$	0.94

that the improvement in survival and chronic lung disease during era 2 may be the result of HFOV causing more uniform lung inflation of the hypoplastic lungs and less ventilator-induced lung injury. A number of experimental studies have demonstrated that a ventilatory strategy that overdistends alveolar units and allows repeated tidal collapse and reopening of damaged lung units might induce lung injury [23]. In animal models, HFOV improves gas exchange, promotes uniform lung inflation, reduces barotrauma and inflammatory mediators and decreases granulocytes in lung lavage samples when compared with conventional ventilation [9, 24, 25]. Since our study was not randomised and the comparison historical, it is possible that factors other than differences in mode of ventilation and type of vasodilator might be in operation. However, there were no differences in the pre or postoperative ventilation indices or blood gases suggesting that the infants in the two eras had comparable lung function. Besides HFOV, the use of a "gentle ventilation and permissive hypercapnia strategy" has been described as improving survival rates in historical series of infants with CDH by trying to minimise barotrauma to hypoplastic lungs [27–29] and this too would support the theory that the reduction in barotrauma in the HFOV group contributed to the improved outcome in era 2.

With the use of prenatal ultrasound to diagnose fetal malformations, it has often been stated that in utero transfer and a planned delivery at a tertiary centre optimizes postnatal care of major fetal abnormalities [1]. However, many of these studies compare institutions that accept in utero transfers with centres that only accept infants transferred after birth. Our series demonstrated a significantly lower survival in infants who were born within the institution compared to those transferred after birth. This may be explained by the fact that none of the infants transferred postnatally had an antenatal diagnosis of CDH, a factor that has recently been associated with improved survival [1]. Survival rates were significantly higher in males than females. This has not been found in other series and may well be a chance finding. Infants requiring vasodilators had significantly increased mortality, which is to be expected as this reflects more severe pulmonary hypertension. We found that associated major malformations were not an important predictor of mortality rate; this could be due to the relatively low incidence in our population and, with improvements in antenatal scanning, pregnancies in which the fetus is found to have multiple major abnormalities often end in termination. We did not find higher mortality rates in right-sided CDH compared to left-sided CDH and this is in line with other studies [20]. Other studies have found that birth weight, Apgar score at 5 min and prenatal diagnosis were statistically significant predictors of survival [26], but these were not confirmed in this study.

The time to surgery was significantly longer in era 2 compared to era 1 ($P = 0.04$). It could be argued that this could have had an effect on increasing survival but we do not believe this to be the case for several reasons. Firstly, there were two infants in era 2 whose operation was delayed for several weeks. Both of these infants died. Removing these two infants from the analysis would mean that the time to surgery between the two eras was no longer statistically significant. Secondly, the criteria for eligibility for surgery were identical between the two eras i.e. stable infants with no inotropic or vasodilator requirement. However, in both the eras, the actual repair of the hernia was performed with the infant on CMV. Hence, during era 2 once stable and off vasodilators and inotropes, infants were changed from HFOV onto CMV and surgery was performed 24–48 h later. This practice may well have increased the time to surgery by 1 or 2 days. Since 2005, our surgeons have successfully operated on infants with CDH while still ventilated using high frequency oscillatory ventilation but these infants are not included in this series.

The only large trial that has looked at the use of NO with CDH is the NINOS trial [13]. This showed a survival rate

of 52% but NO did not decrease the need for ECMO. In our series the overall survival rate was 73% during the period NO was used as the primary pulmonary vasodilator. However, during this time only 30 of the 44 infants actually required NO and the survival in this group of infants was 60% but since the use of NO was not randomised it is impossible to say whether it had any effect on mortality. The value of NO in CDH remains uncertain and this study neither endorses it nor denies its possible role.

Pre-operative ECMO has been used successfully for stabilisation and repairing CDH in many institutions [30]. In our institution ECMO is not immediately available and throughout both eras only four infants with CDH were transferred for ECMO. Hence we cannot compare the survival rate of this study with the studies where need for ECMO has been one of the primary outcomes. However our survival is similar to the 67% published by the multicentre CDH registry involving 2,284 infants treated in 81 neonatal centres with and without ECMO capabilities in six countries [26].

Conclusion

Following initiating elective HFOV and NO, we obtained a survival rate of 73% in infants with CDH over a 10-year period. This survival rate was significantly greater than in similar cases treated in the same unit 5 years previously when CMV and systemic vasodilators were used. We postulate that our improved results are due to the reduction in ventilator-induced lung injury with HFOV compared to CMV and improved recruitment of hypoplastic lungs.

Despite this not being a randomised controlled trial we have continued to use HFOV and NO for infants with CDH admitted to our neonatal unit. The only way to conclusively show a true beneficial effect of one treatment over another is to perform a large multicentre randomised controlled trial. However this would be practically very difficult owing to the low incidence of the disease.

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