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Impact of new treatments for respiratory failure on outcome of infants with congenital diaphragmatic hernia

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Abstract Term and near-term newborn infants with congenital diaphragmatic hernia (CDH), symptomatic in the first 24 h of life or diagnosed antenatally, without other significant malformations were treated at our hospital with high-frequency oscillatory ventilation (HFOV) as a primary modality of ventilation and elective delay in surgical repair after a period of stabilisation. When unresponsive to HFOV, infants were treated with surfactant, inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) to achieve pre-operative stabilisation. From October 1994 to August 1998, 28 newborn infants with CDH were managed with such treatment; mean birth weight was 3184 ± 535 g and gestational age 38.5 ± 1.85 weeks. Age at operation was 68 ± 35 h. In 9 cases, large diaphragmatic defects required the use of a prosthetic patch (Gore-tex). HFOV was used for primary ventilation in inborn patients ($n = 16$); outborn infants ($n = 12$) were placed on HFOV at admittance. A total of 15 patients (53%) were stabilised using only HFOV. Bovine surfactant was administered in 12 infants and 4 responded. iNO was used in eight infants and five responded. ECMO was used in three outborn patients and one survived. Overall, out of 28 infants, 25 survived (89%). Neurological examination (Amiel-Tison and Grenier) of 15 infants showed transient anomalies at 6 months in 40% of infants, while a normal neurological examination was present in all patients at 1 year. The development quotient (Griffiths scales) was within normal values in ten and mildly abnormal in two infants tested at 1 year.

Conclusion Management based on early HFOV, eventually associated with surfactant, iNO and ECMO to achieve preoperative stabilisation, resulted in a good survival rate (89%) and good neurodevelopmental outcome at 1 year of age in infants with CDH.

Key words Congenital diaphragmatic hernia · High frequency oscillatory ventilation · Neurodevelopmental outcome

Abbreviations *CDH* congenital diaphragmatic hernia · *DQ* development quotient · *ECMO* extracorporeal membrane oxygenation · FiO_2 inspired oxygen fraction · *GMDS* Griffiths's mental development scales · *HFOV* high-frequency oscillatory ventilation · *iNO* inhaled nitric oxide · *OI* oxygenation index · SaO_2 oxygen saturation

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Introduction

Management of newborn infants with congenital diaphragmatic hernia (CDH) is evolving due to the development of new modalities of cardiorespiratory support, but the optimal treatment is unknown. The rescue application of innovative and effective techniques of cardiopulmonary support such as extracorporeal membrane oxygenation (ECMO) have not significantly improved the outcome [8, 11]. The iatrogenic injury caused by aggressive ventilation to immature and hypoplastic lungs may be detrimental and, once established, difficult to reverse [14, 19, 22, 24, 28]. From 1994 we have focused our attention on the prevention of lung injury with a gentle pulmonary management strategy rather than on the rescue treatment of infants with damaged lungs, using high-frequency oscillatory ventilation (HFOV) as a primary ventilation mode [31]. Operation was performed electively after a period of pre-operative stabilisation, when the pulmonary vascular bed is more stable and less prone to reactive pulmonary hypertension [4–6, 9, 23, 32]. If pre-operative stabilisation was not achieved with early HFOV, exogenous surfactant, inhaled nitric oxide (iNO) and eventually ECMO were used. In this report we evaluate survival rate and 1 year neurodevelopmental follow up of infants treated with this management strategy.

Materials and methods

A total of 28 consecutive infants at or near term (gestational age >34 weeks) with CDH, symptomatic in the first 24 h of life or diagnosed antenatally, without other significant malformations, were admitted to the level III neonatal intensive care unit and ECMO centre of the Ospedali Riuniti of Bergamo from October 1994 to August 1998. When antenatal diagnosis of diaphragmatic hernia was made, mothers were asked to deliver in our hospital, in order to avoid transport which can be particularly detrimental in such infants. HFOV (Sensormedics 3100 A, Yorba Linda, Calif., USA) was started as a primary ventilation mode in inborn infants and on admission in outborn infants. HFOV was initiated with (FiO_2) = 100%, mean airway pressure 13–15 cm H_2O, amplitude 30–35 cm H_2O, frequency 10 Hz, and an inspiratory time of 33%. Ventilatory settings were modified to obtain a pH between 7.4 and 7.5, PaO_2 80–120 Torr, $SaO_2 > 95\%$, $PaCO_2$ 25–35 Torr and by the extent of lung inflation seen on the chest X-ray. Bicarbonate or Tris-hydroxymethyl-aminomethane buffer were eventually administered to induce a mild metabolic alkalosis. Ampicillin and amikacin were administered as prophylactic antibiotics. The stomach was decompressed with an orogastric tube and central venous and arterial lines were placed. Infants were sedated with fentanyl (2 μg/kg per hour) and midazolam (0.06 mg/kg per hour); paralysis with pancuronium (0.1 mg/kg) was used only during operation and seldom during ventilation. Fluid balance and arterial pressure were carefully monitored; modest fluid restriction (70–90 ml/kg per day) was maintained and haemodynamic support was managed with crystalloids, transfusions and inotropes (dopamine, dobutamine) as needed. Pulmonary haemodynamics and pulmonary blood flow were evaluated with colour-flow Doppler echocardiography.

One dose of bovine surfactant (50 mg/kg Alveofact, Boehringer, Germany) was administered endotracheally if a $FiO_2 > 80\%$ was required to maintain a $PaO_2 > 60$ mmHg. When persistent pulmonary hypertension was detected at echocardiography and the oxygenation index (OI) was greater than 30, iNO was administered, starting at 10 ppm increasing eventually to a maximum of 40 ppm. NO and nitrogen dioxide levels were continuously monitored with an electrochemical analyser (Drager, Lubeck, Germany). Maximum nitrogen dioxide levels of 3 ppm were tolerated. Methaemoglobin levels ware checked twice a day and a maximum level of 4% was allowed. A positive response to NO was considered if PaO_2 increased by 10 mmHg or more and/or SaO_2 increased by 10% or more. After a positive response, weaning from NO was initiated to administer the minimum effective dose.

When infants were unresponsive to the above mentioned treatments and showed acute deterioration (OI > 40 or $PaO_2 < 40$ mmHg). ECMO [2, 7] was offered.

Infants were considered to be stable when they had an optimal blood gas while being weaned from the ventilator with $FiO_2 < 40\%$. The operation was performed as an elective procedure after a careful medical stabilisation, without disconnecting the infant from HFOV. In the last 23 cases, the operation was performed in the neonatal intensive care unit to avoid jeopardising the medical stabilisation by moving the infant to the operating room. Infants on ECMO were operated on whilst on extracorporeal bypass. To reduce bleeding complications, heparin infusion was reduced to maintain an average clotting time of 160–180 s during and for 24 h after surgery and aminocaproic acid was administered before and for 48 h after the operation. During the operation, the hernia was reduced by a transabdominal approach and the defect repaired primarily whenever possible. If a large defect or agenesis of the diaphragm was detected, a prosthetic Gore-tex patch was used. After operation, HFOV was continued, switching to conventional ventilation when the required FiO_2 was lower than 30%. Before discharge an EEG, cranial ultrasonography, and an ophthalmological examination, were performed. If abnormalities were detected on cranial ultrasonography, MRI or CT should be performed. Infants were considered to be surviving when they were discharged home. The surviving infants were included in the neurodevelopmental follow up at 6, 12, 24 and 36 months. The neurological examination was done by a paediatric neurologist and psychiatrist using the Amiel-Tison and Grenier Neurological Evaluation [1] and Griffiths's Mental Development Scales (GMDS) [15]. Using the GMDS a general development quotient (DQ) was calculated from the mean of five subquotients: locomotor, personal/social, hearing and speech, eye-hand co-ordination, performance. Three categories of infants were identified: (1) normal: no abnormal neurological signs and DQ > 85; (2) mildly abnormal: abnormal neurological signs but not cerebral palsy and DQ 84–50; and (3) severely abnormal: cerebral palsy, hearing deficiency requiring prosthesis, serious visual deficiency, ensemble of minor sequelae, DQ < 50.

Results are given as mean and standard deviation or as median (range) where the distribution is where significantly skewed.

Results

Patient characteristics are shown in Table 1. Antenatal diagnosis was made in 16 newborns whose gestational age at diagnosis varied from 18 to 34 weeks. Of those

Table 1 Patient characteristics

n	28
Birth weight (g) (mean and SD)	3184 ± 535
Gestational age (weeks) (mean and SD)	38.5 ± 1.85
Prenatal diagnosis (*n*) (%)	16 (57)
Stomach in chest (*n*) (%)	18 (64)
Hernia left/right	23/5
Gore-tex patch (*n*) (%)	9 (32)
Hours at operation (mean and SD)	68.61 ± 35.89
Survived (*n*) (%)	25 (89)

Table 2 Duration of high-frequency oscillatory ventilation (*HFOV*), inhaled nitric oxide (*iNO*), extracorporeal membrane oxygenation (*ECMO*), intubation and hospital stay (mean and SD)

HFOV duration (h)	217 ± 107.2
iNO duration (h)	97 ± 73
ECMO duration (h)	293.3 ± 61.58
Duration of intubation (days)	19.5 ± 9
Hospital stay (days)	41.29 ± 26.19

infants, 12 infants showed respiratory distress in the first hours of life. A total of 16 infants were inborn and 12 were referred from other hospitals; no infant died during transport. Apgar score at 1 min was 5 ± 2, at 5 min 7 ± 1. The mean of the best OI in the first 24 h was 19 ± 13. Infants were on HFOV for 217.6 ± 107.2 h, then they switched to conventional ventilation. Prosthetic patches were required to cover large defects in nine infants. All infants were stable during operation and in the postoperative period; none showed air-leak syndromes. A positive response to HFOV was shown by 15 patients (53%) and were stabilised using only this mode. One dose of surfactant was administered to 12 infants and 4 responded. Treatment with iNO was necessary for eight infants and five showed a progressive increase of PaO_2 and SaO_2 allowing reduction of FiO_2 and ventilator settings. Three outborn patients fulfilled ECMO criteria at the referring hospitals. HFOV, surfactant and iNO were attempted at the time of admission, but infants were unresponsive and underwent extracorporeal life support. Two infants died of pulmonary haemorrhage after 14 and 15 days of bypass, respectively. The third ECMO patient did not respond to iNO before ECMO; after 9 days of veno-arterial bypass the infant was successfully decannulated and responded well to iNO and HFOV. Twenty-three infants were discharged home, two were transfered to the referring hospital after weaning from ventilation. Out of 28 patients, 25 (89%) survived. No late deaths have occurred so far. Data of 1 year neurodevelopmental outcome of the first 15 patients (10 males and 5 females) are available at present; 7 infants (46%) were outborn, 8 (64%) inborn. All the infants were treated with HFOV, 3 with iNO and 1 with ECMO.

At discharge, EEG was normal in 13 infants; two infants were transferred to the referring hospital before performing EEG. Cranial ultrasound was normal in 13 infants; two infants, included the one treated with ECMO, showed an extra-axial fluid collection which was not detected at 6 months. No infant was evaluated with MRI or CT. Ophthalmological examination was normal in all 15 infants.

Discharge neurological examination was normal in nine infants (60%); three infants (20%), including the one treated with ECMO, showed a diffuse hypotonia, two (13%) a retardation of motor and postural pattern, and one (7%) choreic movements of the extremities.

At 6 months, the neurological examination was normal in nine infants (60%), while the six infants continued to present the mild anomalies detected at discharge.

Table 3 Neurodevelopmental outcome in 12 survivors after repair of congenital diaphragmatic hernia at 1 year of age. (*GMDS* Griffiths's Mental Developmental Scales)

Index	Mean (SD)	Range
GMDS quotient	98 (14.19)	75–128
Subquotients		
Locomotor	105 (15.6)	70–125
Personal and social	104 (18.17)	75–135
Hearing and speech	88 (25.65)	66–150
Eye-hand co-ordination	94 (13.98)	70–121
Performance	95 (15.43)	83–120

At the age of 12 months, neurological examination was normal in all 15 patients including those with mild neurological anomalies at 6 months.

The GMDS general quotient for 12 patients at the age of 1 year was 98, (range 75–128). This was derived from five subquotients represented in Table 3.

Two infants who presented mild neurological anomalies at 6 months showed no neurological signs but a mildly abnormal DQ (75 and 83). No infant showed severe neurodevelopmental abnormalities.

Discussion

A management strategy based on early HFOV and preoperative stabilisation allowed us to achieve a survival rate of 89% in our population of newborn infants with CDH. Survival rate has increased compared with our previous experience: in a similar population of patients treated with conventional ventilation and early operation between 1991 and 1994 survival rate was 61% [27]. Surfactant, ECMO and iNO were introduced in different time periods in the first group of patients. In 1994 HFOV became available and the new management strategy was started. No significant changes of the general supportive care between the two groups were introduced. CDH is one of the most difficult conditions to treat in the neonatal period; the associated mortality rate is mainly related to pulmonary hypoplasia and biochemical immaturity of the ipsilateral and contralateral lungs [8, 11, 20, 22]. An increasing body of evidence indicates that conventional mechanical ventilation may be responsible for lung damage which can predispose to multi-organ failure and eventually to death. [16, 19, 24, 28]. The iatrogenic lung injury of CDH infants may occur rapidly and be detrimental and difficult to reverse once established. The introduction of ECMO did not dramatically improve the survival rate of CDH infants, as indicated in the International Neonatal ECMO Registry Report [11] and in an European multicenter study [29]. However, ECMO is often offered to the sickest infants after the lung injury has probably impaired lung function or to infants with a fatal pulmonary hypoplasia. A gentle ventilatory approach using early HFOV can allow effective gas exchange while limiting lung injury [31]. In our CDH population, 53% of patients were stabilised using only HFOV; none of the 16

inborn patients treated with early HFOV required extracorporeal life support. ECMO was offered to three outborn infants, fulfilling entry criteria at the referring centres. The potential role of surfactant is difficult to assess; we do not know whether the few patients who did respond to surfactant might not have also responded to a more aggressive recruitment strategy with HFOV. Operation was delayed after careful medical stabilisation; the benefits of pre-operative stabilisation are largely reported in the literature [4–6, 9, 13, 23, 25, 26, 32]. At discharge, no infant showed chronic lung disease requiring oxygen administration at domicile. The preliminary data of neurodevelopmental outcome are also encouraging: while 40% of patients showed transient mild anomalies at discharge and at 6 months of age, neurological examination was normal in all infants tested at 1 year. Mean DQ was within the reference range in 84% of infants. Infants with CDH seems to experience a number of neurodevelopmental abnormalities at 1 year: Nobuhara reported an incidence of development delay in infants with CDH of 37%; of the infants exhibiting a mild to moderate developmental delay, 72% were treated with ECMO [12]. A study by Van Meurs et al. [30] focussed specifically on the outcome of ECMO-treated CDH infants; 58% of the group were reported to be normal between 1 year of age whereas 25% had suspected development delay and 17% were abnormal. Bernbaum et al. [3] reported that CDH infants encountered a greater number of neurodevelopmental abnormalities during the 1st year of life; this is probably related to the severity of the primary illness itself or the variables associated with prolonged ECMO therapy. Treatment of infants with CDH is still in evolution and there is no agreement on optimal strategy. Many single reports claim improved survival rate of CDH patients using different strategies for therapy including conventional ventilation [25, 32], HFOV [21], ECMO [2, 4, 5], and iNO [18]. However, conclusions regarding the best treatment are of limited value due to the small number of patients in such studies [17]. The CDH Study Group was formed in the attempt to collect multi-institutional data in an international registry, but difficulties in data interpretation still exist; after considering 461 patients from 62 worldwide institutions, the CDH Study Group realised that there was a tremendous diversity in management strategies for patients with CDH and suggested the need for carefully conducted multicentre studies to determine the best treatment strategies for infants with CDH [8]. We believe that good management is often a combination of more than one technique. In our infants with CDH, a management strategy with a conservative ventilatory approach using HFOV as a primary ventilation mode, the eventual use of surfactant, iNO and ECMO to achieve pre-operative stabilisation allowed us to obtain a good survival rate and a good 1-year neurodevelopmental outcome for the survivors. Careful long-term follow up is required to evaluate this high risk population of infants.

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