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CPAP combined with inhaled nitric oxide for treatment of lung hypoplasia and persistent foetal circulation due to prolonged PPROM

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ABSTRACT

Background: Second trimester preterm premature rupture of the membranes (PPROM) before 24 weeks of gestation is associated with a high morbidity and mortality rate.
Aim: To demonstrate the efficacy of early continuous positive airway pressure (CPAP) combined with inhaled nitric oxide (iNO) for treatment of preterm infants with lung hypoplasia and persistent foetal circulation (PFC) due to very early PPROM and prolonged severe oligohydramnios.
Methods: Seven infants with prolonged PPROM, lung hypoplasia, respiratory distress and persistent foetal circulation were intubated in the delivery room for subsequent surfactant and iNO application. As our new treatment strategy was to keep the period of mechanical ventilation as short as possible, all infants were switched on nasal CPAP combined with iNO within the first 24 hours.
Results: Mean gestational age at PPROM was 19 + 6 weeks (range 14 + 2 to 23 + 6 weeks) and the average latency period between rupture of membranes and delivery was 10 + 3 weeks (7 + 3 to 16 + 4 weeks). Infants were born at 30 + 3 weeks of gestation (28 + 3 to 33 + 1 weeks) with an average birth weight of 1468 g (884 to 2200 g). In all neonates CPAP combined with iNO reversed PFC and 6 patients stabilised without the need for reintubation and mechanical ventilation. One infant had to be reintubated following 12 hours of CPAP combined with iNO due to respiratory insufficiency. All seven infants survived to discharge.
Conclusion: CPAP combined with iNO might be a promising approach for therapy of preterm infants with lung hypoplasia and persistent foetal circulation due to very early PPROM.

1. Introduction

Second trimester preterm premature rupture of the membranes (PPROM) before 24 weeks of gestation is associated with a high morbidity and mortality rate [1,2]. Gestational age at PPROM and the latency period between rupture of membranes and delivery are significant risk factors for the development of pulmonary hypoplasia, which is associated with a poor neonatal outcome [2]. However, it is increasingly recognised, that many infants with pulmonary hypoplasia have an element of reversible pulmonary hypertension that is sensitive to inhaled nitric oxide (iNO) therapy [3–5]. Furthermore, animal data suggest that iNO therapy enhances distal lung growth and promotes pulmonary vascular angiogenesis [6]. Therefore, current neonatal treatment strategies for lung hypoplasia and persistent foetal circulation (PFC) include mechanical ventilation, surfactant application and iNO [7–9].

However, it is questionable whether mechanical ventilation is the best treatment option for preterm infants with hypoplastic lungs. Respiratory failure due to PPROM is at least in part related to impaired lung perfusion and mechanical ventilation may aggravate this problem. Besides, such infants usually require extensive ventilation pressures with a high risk for lung damage and pneumothorax [8].

Continuous positive airway pressure (CPAP) represents a therapeutic option for infant respiratory distress syndrome (IRDS) first described by Gregory et al [10]. Meanwhile there have been many reports about the positive effect and advantages of CPAP for treatment of IRDS [11]. However, until now CPAP has only been used in milder cases of respiratory distress related to early PPROM, while patients with more severe RDS usually get intubated and mechanically ventilated. In case of persistent foetal circulation, mechanical ventilation is combined with iNO [7,9].

In this retrospective study we investigated, whether CPAP combined with iNO could be a treatment option for high risk infants with lung hypoplasia and persistent foetal circulation due to very early PPROM < 24 weeks of gestation.

2. Patients and Methods

The study was approved by the Ethical Review Board of the Medical Faculty of the University of Bonn. We identified all pregnancies delivered at the Department of Obstetrics and Prenatal Medicine of the University of

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Bonn from January 2007 to September 2009 with PPROM before 24 weeks of gestation. Our retrospective analysis included all live birth infants with PPROM<24 weeks of gestation, documented prolonged severe oligohydramnios with a latency period>6 weeks, clinical signs of lung hypoplasia and persistent foetal circulation. The gestational age at rupture of membranes was calculated from the first day of the last menstrual period, confirmed and adjusted if necessary by first-trimester antenatal ultrasound. Severe oligohydramnios was defined as an amniotic fluid index (AFI)<3. The latency period was the difference between the gestation at membrane rupture and delivery.

All infants revealed severe respiratory distress and were intubated in the delivery room. Subsequently 100 mg/kg surfactant (Curosurf, Chiesi GmbH, Hamburg, Germany) was applied via the INSURE (**In**tubation **SUR**factant **E**xtubation) procedure or followed by a short period of mechanical ventilation. Inhaled nitric oxide (INOmax®, INOvent, Linde Gas Therapeutics, Munich, Germany) was started within one hour after delivery following diagnosis of persistent foetal circulation by either a preductal and postductal pulse oxymetric oxygen saturation (SpO2) gradient>10% or by echocardiography demonstrating right to left shunting.

As our new treatment strategy was to keep the period of mechanical ventilation as short as possible, all infants were switched on nasal CPAP (Infant Flow, Electro Medical Equipment, Brighton, UK) combined with iNO (INOmax®, INOvent, Linde Gas Therapeutics, Munich, Germany) within the first 24 hours. Extubation was performed without formal extubation criteria except a stable respiratory drive, as we hypothesised that CPAP reduces the negative impact of mechanical ventilation on venous return, right ventricular output and pulmonary blood flow. The injector module of the INOvent delivery system was placed at the beginning of the inspiratory limb between the Infant Flow driver and a humidifier. Fraction of inspired oxygen (FiO2), nitric oxide (NO) and nitrogen dioxide (NO2) levels were continuously monitored at the end of the inspiratory limb. Inhaled nitric oxide was initiated at 20 ppm and subsequently decreased according to echocardiographic and clinical improvement. FiO2 was started with 1.0 and adjusted to reach a preductal oxygen saturation>92%. Failing criteria of CPAP / NO with the need for reintubation included continuing PFC, a preductal oxygen saturation<92% despite a FiO2 of 1.0 or hypercapnia with a blood pH<7.25.

Analysed outcome parameters were survival to hospital discharge, pneumothorax diagnosed by chest radiograph, bronchopulmonary dysplasia (BPD) defined as oxygen or ventilatory support at 36 weeks of gestation, intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL) and retinopathy of prematurity (ROP).

3. Results

We identified 49 pregnancies within the study period with confirmed PPROM between 13 and 23 weeks of gestation. Seventeen pregnancies were either miscarried or terminated. Of the remaining 32 pregnancies, 7 neonates met the selection criteria including PPROM<24 weeks of gestation, prolonged severe oligohydramnios with a latency period>6 weeks, lung hypoplasia and persistent foetal circulation. All 7 patients received prenatal betamethasone at the gestational age of 24 weeks. Patients`characteristics are demonstrated in Table 1. Mean gestational age at PPROM was 19+6 weeks (range 14+2 to 23+6 weeks) with an average latency period between rupture of membranes and delivery of 10+3 weeks (range 7+3 to 16+4 weeks). Weekly follow up scans were performed in all cases and demonstrated persisting severe oligohydramnios (deepest pocket<2 cm; AFI<3) throughout the latency period. Infants were born at 30+3 weeks of gestation (range 28+3 to 33+1 weeks) with an average birth weight of 1468 g (range 884 to 2200 g).

Four patients received surfactant via INSURE, while three patients remained mechanically ventilated for some hours following surfactant application. All seven infants received iNO within the first hour following surfactant application. Table 2 summarises the respiratory course. All infants were extubated and switched on nasal CPAP (5-8 cm H2O) combined with iNO within the first 24 hours after delivery. In all neonates CPAP combined with iNO reversed PFC. Six patients stabilised with this therapeutic concept without the need for reintubation and mechanical ventilation. They required 3.5 days (range 2 to 6 days) of CPAP combined with iNO and another 21 days (range 9 to 62 days) of CPAP without iNO. Nitrogen dioxide (NO2) levels as well as methemoglobin values remained at all times in a non toxic range (NO2<0.5 ppm and methemoglobin<3% respectively).

Table 1
Patients characteristics.

Patient	Gestation at PPROM (weeks)	Latency period (weeks)	Gestation at delivery (weeks)	Birth weight (g)	APGAR 1/5/10 min
1	18+2	10+1	28+3	884	7/8/8
2	22+5	7+4	30+2	2200	7/8/9
3	20+1	9+0	29+1	1335	3/5/7
4	19+6	10+0	29+6	1650	5/6/7
5	20+5	12+3	33+1	1730	5/7/8
6	14+2	16+4	30+6	1040	8/9/9
7	23+6	7+3	31+2	1440	7/8/8

Patient 6 had to be reintubated following 12 hours of CPAP combined with iNO due to respiratory insufficiency. Hypercapnia stabilised with high frequency oscillatory ventilation (HFOV) in combination with iNO. However, applying a mean airway pressure (MAP) of 12-13 cmH20 the infant continued to require 0.8-1.0 FiO2 to reach an oxygen saturation>90%. It took a second and third course of surfactant to improve the respiratory situation and the ventilation parameters gradually decreased to a mean airway pressure of 8-10 cmH2O and 0.3 FiO2 during the following days. Persistent foetal circulation also improved and we were able terminate iNO after 6 days. The infant was finally extubated and switched to CPAP after seven days of HFOV.

All seven infants survived to discharge. Secondary outcome parameters revealed that patient 5 developed pneumothorax in the first hours of life while he was mechanically ventilated. Patient 1 and patient 6 developed BPD, both were discharged home on oxygen. None of our patients revealed IVH, PVL or ROP.

4. Discussion

Recently, Lindwall et al reported for the first time the feasibility to combine CPAP with nitric oxide [12]. Subsequently they could demonstrate that CPAP combined with iNO significantly improves oxygenation in preterm infants with moderate respiratory distress syndrome [13]. In an additional study they described, that the contribution of nitrogen oxides from treatment to workplace air were minor compared to those from ambient air [14].

Our study is the first report on the combination of CPAP with iNO for treatment of lung hypoplasia and persistent foetal circulation in

Table 2
Respiratory course after immediate intubation in the delivery room with subsequent surfactant application.

Patient	Age of starting CPAP+iNO	Total days of CPAP+iNO	Subsequent days of CPAP without iNO
1	20 min	3	62
2	15 min	6	20
3	45 min	5	9
4	10 hours	3	11
5	15 hours	2	10
6	11 hours	0.5 (→ reintubation)	86
7	50 min	2	12

Only patient no 6 had to be reintubated following 12 hours of CPAP combined with iNO due to respiratory insufficiency with hypercapnia. Following 7 days of mechanical ventilation (including 6 days of iNO therapy) the infant was extubated and switched on CPAP.

infants with very early PPROM prior 24 weeks of gestation and a prolonged period of severe oligohydramnios.

Respiratory insufficiency in preterm infants with very early PPROM and a prolonged latency period is at least in part related to impaired lung perfusion. Therefore, therapeutic strategies should also focus on improvement of lung perfusion next to provision of respiratory support. However, mechanical ventilation increases the intrathoracic pressure causing a decrease in venous return, right ventricular output and pulmonary blood flow [15]. Besides, mechanical ventilation is a known risk factor for many complications of prematurity like intraventricular haemorrhage or bronchopulmonary dysplasia [16,17]. Animal data suggest that in preterm infants the period of mechanical ventilation should be kept as short as possible. Even a few days of mechanical ventilation are associated with an increased inflammatory response in the lungs, a weaker respiratory drive, peribronchiolar alveolar wall thickening and a higher risk for cerebral injury [18,19].

CPAP is a well-established therapeutic approach for treatment of infant respiratory distress syndrome [11]. We thought that it might also be advantageous for preterm infants with lung hypoplasia and persistent foetal circulation, as it represents a lung protective therapy with minor effects on pulmonary perfusion compared to mechanical ventilation. We combined CPAP with iNO for treatment of persistent foetal circulation and yielded a good outcome for our high risk infants. Six of seven patients could be stabilised on CPAP combined with iNO without the need for reintubation. The only infant requiring reintubation revealed a very early PPROM at 14 + 2 weeks of gestation with a latency period of more than 16 weeks. Following 12 hours of CPAP combined with iNO (FiO2 0.8-1.0) the infant suffered from respiratory fatigue with hypercapnia. High frequency oscillatory ventilation (HFOV) combined with iNO decreased carbon dioxide values to 50-60 mmHg. However, mechanical ventilation did not improve oxygenation and the infant continued to require a high FiO2 of 0.8-1.0 for several days. Persistent oxygenation problems might reflect the circumstance, that impaired lung perfusion considerably contributed to the patients` respiratory insufficiency.

Overall CPAP combined with iNO seems to be promising new therapeutic approach. Our study demonstrates that iNO can be effectively applied to preterm infants with lung hypoplasia and PFC in combination with CPAP. In the 1990 s mortality rates for infants with rupture of membranes before 24 weeks ranged around 40% to 90% depending on the gestation at PPROM [20–22]. Three recent studies could demonstrate improved neonatal outcome using HFOV, surfactant and iNO. However, mortality rate still ranged between 27% and 32% and more than one third of the survivors revealed chronic lung disease [7–9]. In our study all patients with comparable inclusion criteria survived and only two infants (29%) exhibited chronic lung disease. Only one infant (14%) suffered pneumothorax while he was mechanically ventilated. Everest et al and Lindner et al reported a pneumothorax incidence of 25% and 53%, respectively [7,8].

There have been a few case reports about a condition called “dry lung syndrome after oligohydramnios”, which can mimic true lung hypoplasia and is characterized by a dramatic respiratory improvement within 24-36 hours of life [23–25]. However, most of these patients with dry lung syndrome experienced PPROM after 24 weeks of gestation, while our study population suffered PPROM at a mean gestational age of 19 + 6 weeks. Furthermore, our patients revealed a latency period until delivery of >6 weeks, while patients with dry lung syndrome usually exhibited a latency period <3 weeks. As gestational age of rupture of membranes and latency period are important predictors of pulmonary hypoplasia [2], it is very likely that our patients revealed no dry lung syndrome but rather true lung hypoplasia. Besides all our patients revealed persistent foetal circulation, a complication that has rarely been described in dry lung syndrome.

The results of our analysis are limited due to the small sample size of seven patients, the retrospective character of the study and a missing control group. However, in conclusion the data presented support the hypothesis that CPAP combined with iNO might improve the outcome of preterm infants with lung hypoplasia and persistent foetal circulation due to very early PPROM. A randomized controlled trial is needed to compare CPAP/NO with conventional treatment strategies using mechanical ventilation/NO. Such a study should also focus on the question whether CPAP combined with iNO works mainly in cases with moderate lung hypoplasia or also in infants with severe lung hypoplasia.

Conflict of interest

No author has any conflicts of interest.

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