Spontaneous breathing and respiratory support of preterm infants at birth

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CHAPTER 8

A randomized controlled trial of delivery room respiratory management in very preterm infants

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Abstract

Background. Initial ventilation strategy may play an important role in the development of bronchopulmonary dysplasia (BPD) in very preterm infants. Early nasal continuous positive airway pressure (CPAP) is an accepted approach, but randomised clinical trials are lacking. Our aim was to determine whether early nasal CPAP, preceded by a sustained inflation, is more effective and less injurious in very preterm infants than conventional intervention.

Methods. Two hundred and seven very preterm infants were randomly assigned in the delivery room to either a sustained inflation through a nasopharyngeal tube followed by early nasal CPAP (early functional residual capacity intervention) or repeated manual inflations with a self-inflating bag and mask followed by nasal CPAP, if necessary, after arrival at the neonatal intensive care unit. Primary outcome measure was intubation < 72 hours of age and bronchopulmonary dysplasia at 36 weeks was used as secondary outcome. This trial is registered as the early functional residual capacity intervention trial (ISRCTN 12757724).

Results. In the early functional residual capacity intervention group fewer infants were intubated < 72 hours of age (OR 0.57 (95%CI 0.32-0.98)) or received more than 1 dose of surfactant (OR 0.39 (95%CI 0.18-0.88)) and the average duration of ventilatory support was less (median days (IQR): 2.7 (0.5-10) vs 4.3 (0.5-20); P = 0.01). Infants in the early functional residual capacity intervention group developed less BPD (OR 0.41 (95%CI 0.18-0.96)).

Conclusion. A sustained inflation followed by early nasal CPAP, delivered through a nasopharyngeal tube, is a more efficient strategy than repeated manual inflations with a self-inflating bag and mask followed by nasal CPAP on admission to the NICU.

Introduction

The pathogenesis of bronchopulmonary dysplasia (BPD) or chronic lung disease in very preterm infants is multifactorial, but ventilator-induced lung injury plays a major contributing role (1). Various new ventilation strategies have been introduced, but this has not reduced the incidence of BPD (2). Early respiratory management, i.e. ventilatory support from birth during the first days of life, may influence pulmonary outcome, but, due to lack of data, there is no consensus on the early respiratory management of preterm infants (3). Retrospective cohort and experimental studies suggest that the initial ventilation strategy may play an important role in the development of BPD (4-9). The most effective and least injurious way to recruit the lung in preterm infants at birth may be a combination of a sustained inflation and early nasal continuous positive airway pressure (CPAP). This attempt to avoid intubation and mechanical ventilation, may reduce lung injury and BPD in preterm infants as suggested in a retrospective study by Lindner et al (10). A trial of early nasal CPAP at birth seems justified in infants at risk of respiratory distress syndrome (RDS), providing early surfactant rescue is given if required (11;12). We performed a randomized controlled trial and compared the traditional respiratory approach with a new method that combined a number of techniques, which theoretically could improve the respiratory outcome of preterm infants. We hypothesized that a sustained inflation followed by early nasal CPAP, using a pressure-limited mechanical device, is a more effective and less injurious management strategy in preterm infants than conventional intervention.

Patients and Methods

The limits of viability in the Netherlands are set at 25 weeks' gestation. All very preterm infants < 33 weeks' gestation, born in the Leiden University Medical Center were eligible for this study if they were free from known major congenital anomalies. The study was approved by the Ethics Review Committee of the hospital. Patients were included before birth and informed consent was obtained from the infant's parents or legal guardian. Before birth patients were assigned randomly to early functional residual capacity intervention (EFURCI) or conventional intervention by using sealed envelopes. Blocked randomization and stratification for each week of gestational age were used to ensure treatment balance between the two arms.

EFURCI-approach

After oropharyngeal and nasal suctioning (time = 0-30 seconds), and if breathing was insufficient (i.e. no signs of spontaneous breathing or spontaneous breathing present, but signs of poor air-entry (severe retractions, nasal flaring), a pressure limited (20 cm H_2O) inflation was sustained for 10 seconds, using a nasopharyngeal tube and a T-piece ventilator (Neopuff Infant Resuscitator, Fisher and Paykel, New Zealand) (time = 30-45 seconds). This T-piece ventilator is a pressure-limited mechanical device which supplies a consistent peak

inspiratory pressure and positive end-expiratory pressure (PEEP) and is capable of delivering a sustained inflation (13-16). Use of a sustained inflation reduces the need for higher initial airway pressures. To avoid leakage, a nasopharyngeal tube was used as interface (17). Nasopharyngeal tubes with a diameter of 2.5-4.0 mm were used, according to gestational age/ birth weight. The length of the tube was cut down to 6 cm. The mouth and other nostril were held closed manually during the inflation. This procedure was repeated (time = 50-65 seconds) with an increased peak inspiratory pressure (25 cm H_2O) if breathing remained insufficient and/or the heart rate was < 100 beat per minute and/or the infant was cyanotic. After the initial inflation, early nasal CPAP at 5 to 6 cm H_2O was started. If breathing was sufficient, the patient was observed in the delivery room before transportation to the NICU. If there was improvement (heart rate >100 beats per minute and pink colour, but apnea or insufficient breathing), intermittent ventilation with a peak inspiratory pressure of 20 to 25 cm H_2O and a rate of 60 per minute was delivered through the nasopharyngeal tube for several minutes until the infant improved (heart rate >100 beats per minute, pink colour and spontaneous breathing). Endotracheal intubation and mechanical ventilation was initiated if the heart rate did not increase above 100 beats per minute, the infant remained cyanosed, breathing was absent, or marked dyspnoea occurred (time = 90 seconds-5 minutes). Patients were transferred to the NICU with early nasal CPAP or Intermittent Positive Pressure Ventilation.

Conventional intervention group

In this group a self-inflating bag and mask with a built-in pressure limitation (Ambu Baby R Resuscitators, Ambu, Ballerup, Denmark) and an oxygen reservoir were used after birth. A manometer was attached to monitor the pressures given. The mask and bag deliver inconsistent PIP and minimal PEEP and are unable to deliver a sustained inflation (14;18;19). With this approach a higher initial pressure is used to open the lung and early nasal CPAP was only given on arrival in the NICU if needed. Mask and bag ventilation was administered during 30 seconds if breathing was insufficient after oropharyngeal and nasal suctioning (time = 30-60 seconds). Initial inflation pressures of 30-40 cm H_2O were used, after that not more than 20 cmH_2O was allowed (3). If breathing remained insufficient, or the heart rate was <100 beats per minute, or the infant remained cyanotic, or inflation was not possible, endotracheal intubation and mechanical ventilation were performed (time = 60-90 seconds). If bag and mask resuscitation was successful and breathing was sufficient (spontaneous breathing, normal chest movements, no cyanosis, heart rate >100 beats per minute), the infant was observed in the delivery room and transferred to the NICU. Nonintubated infants were transferred with oxygen monitored by measuring oxygen saturation.

In both groups

One hundred percent oxygen was initially used and weaned down as quickly as possible depending on the infants' response, colour and heart rate. Pulse oximetry was started

immediately after resuscitation. If no respiratory support in the delivery room was needed, the infant was observed and transferred to the NICU. Nasal CPAP was started if there were signs of respiratory distress or the FiO_2 was > 0.3. Infants on (early) nasal CPAP were placed on an Infant Flow Device (EME Tricomed, Brighton, UK) or Infant Star ventilator (Infrasonics Inc., San Diego, CA, USA) with Hudson prongs (Hudson-RCI, Temecula, California, USA). The level of pressure was titrated from 5 to 8 cmH_2O according to the degree of respiratory distress, assessed by observing chest retractions, effort of breathing, chest radiograph, and oxygen requirement (PaO_2 > 50 mmHg, while pH > 7.20 and $PaCO_2$ < 60 mmHg).

Caffeine or theophylline were given as soon as possible after birth to infants < 30 weeks of gestation and in more mature infants if they had apnea. Arterial and transcutaneous partial pressures of oxygen and carbon dioxide and oxygen saturation were monitored. RDS was defined in the presence of clinical features (need of supplemental oxygen, sternal retraction, intercostal and subcostal recession, grunting and tachypnea) and radiological finding of poor lung expansion. Chest X-rays were used to assess the severity of RDS and lung expansion. Chest X-rays were reviewed by a radiologist and the reading was recorded in the database. The radiologist did not participate in this trial, only the usual clinical information was given, and he/she was not aware of the treatment assignment. Intubation and mechanical ventilation were initiated either when the arterial oxygen saturation values were < 88% or $PaO_2 \leq 50$ mmHg while receiving $FiO_2 \geq 0.40$ (corresponding with an $AaPO_2$ ratio <0.22), or the $PaCO_2$ was > 60 mmHg, with a pH < 7.20, or there were more than 4 apnoeic episodes in one hour or the infant needed > 2 episodes of bagging per hour. These criteria were agreed on by participating clinicians before the study started and were applied rigorously. The decision was made by clinicians other than the investigators. Whenever one of the investigators was supervising the NICU, one of their colleagues (fellows) made the decision to intubate or not in the infants included in the study. Surfactant (Curosurf, Chiesi, Italy) was given at 12 hour intervals when on mechanical ventilation with a mean airway pressure x FiO_2 ratio > 2. All infants intubated in the delivery room received surfactant shortly after arrival in the NICU, if required. All infants intubated later on in the NICU received surfactant shortly after intubation if required. Infants were extubated as soon as the FiO_2 was less than 0.3 and the mean airway pressure < 7 cm H_2O. Immediately after extubation nasal CPAP was started. Nasal CPAP was discontinued when the neonate remained stable with a capillary PCO2 < 60 mmHg, oxygen saturation > 92% without supplementary O_2. When taken off nasal CPAP, infants were given supplemental oxygen using low flow nasal cannulae if saturation < 92%. If oxygen requirements exceeded 30% (effective FiO_2 (20)), nasal CPAP was restarted.

The primary outcome measure was the percentage of infants intubated within 72 hours of age. Secondary outcome measures were intubation in the delivery room, the need for mechanical ventilation and surfactant treatment, death during admission or BPD based

on the National Institute of Child Health and Human Development (NICHD) definition (21), intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), retinopathy of prematurity (ROP), persistent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC). All infants had cerebral ultrasounds done at least three times in the first week and weekly thereafter.

Data are reported as means and SDs or as medians and interquartile range (IQR) if appropriate. Sample size analysis showed that to detect a reduction in intubation and mechanical ventilation from 60% to 40%, with a power of 80% and an a error of 5% (two tailed test), 97 infants were required for each arm of the study. As our center admits about 200 eligible newborns per year and we expected 20% of the parents to refuse consent, the duration of the study was estimated at 1 year and 3 months. All analyses were performed on an intention-to-treat principle. The baseline characteristics and outcome parameters in the 2 treatment groups were compared using Student's t test for parametric and the Mann-Whitney U test for non-parametric comparisons for continuous variables, and the $\chi 2$ test for categorical variables. Reported P values are two-sided, and $P < .05$ was considered statistically significant. The presented odds ratio (OR) with the corresponding 95% confidence interval is an approximation to the relative risk.

This study was approved by the Leiden University Medical Center Ethics Review Committee.

Results

A total of 217 inborn very preterm infants (gestational age: 25-32 weeks) were admitted to the NICU between April 1, 2005 and July 12, 2006. Five infants were excluded because of severe cardiac or respiratory anomalies or syndromes incompatible with survival. Five were not included because their parents did not consent antenatally. The early respiratory management of the 207 infants is shown in Fig 1. The demographic characteristics of both groups are presented in Table 1.

Fewer infants in the EFURCI group were intubated within 72 hours of age (38/104 (37%) vs. 52/103 (51%); P = .04; OR 0.57 (95% CI 0.32-0.98). In the EFURCI group 73 (70%) of 104 infants needed a prolonged inflation, 44 (60%) of 73 infants could be stabilized after inflation of 20 cmH_2O, 29 (40%) of 73 needed a second inflation of 25 cmH_2O, and 18 of these 29 (62 %) infants also needed intubation. Nasal intermittent positive pressure ventilation optional after sustained inflation in case of absent/insufficient breathing, was used in 15 (14%) of 104 infants. Almost all of these infants (13 of 15) had to be intubated in the delivery room.

Secondary outcomes are shown in Table 2. The duration of ventilatory support (including nasal CPAP) was shorter in the EFURCI group compared to the conventional group (median

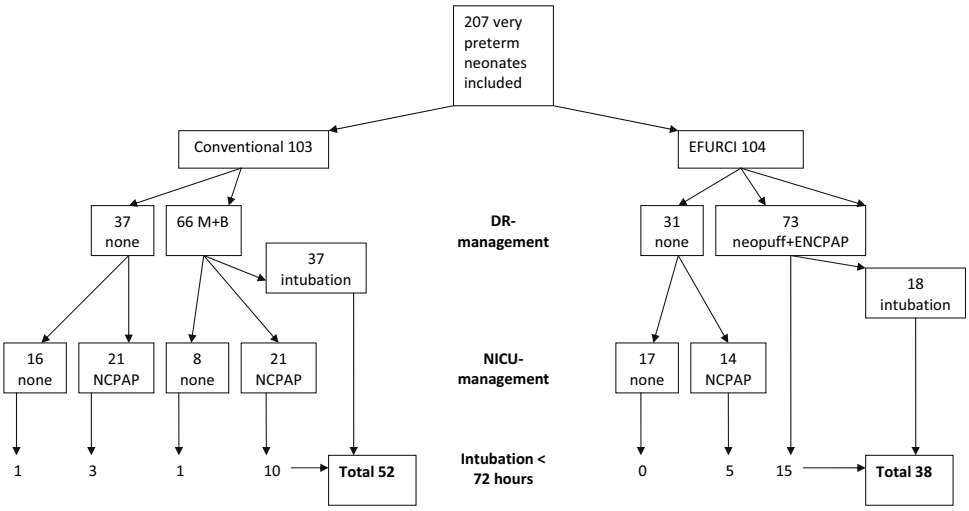

Figure 1. Early respiratory management of the two trial groups.

Table 1. Demographic characteristics.
Chorioamnionitis: maternal fever with at least one of the following symptoms: leucocytosis, tenderness of the uterus, fetal tachycardia, foul-smelling amniotic fluid; antenatal steroids: any number of doses of steroids for induction of fetal lung maturation; PPROM = preterm premature rupture of the membranes; IUGR = intra uterine growth retardation.

Characteristic	EFURCI N = 104	Conventional N = 103
Birthweight, grams, mean (SD)	1311 (403)	1290 (392)
Gestational age, weeks, mean (SD)	29.4 (1.9)	29.5 (1.9)
Male gender, n (%)	56 (54)	57 (55)
Umbilical arterial pH, mean (SD)	7.25 (0.09)	7.25 (0.10)
Prenatal steroids, n (%)	85 (82)	83 (81)
Chorioamnionitis, n (%)	12 (12)	8 (8)
PPROM, n (%)	21 (20)	28 (27)
(Pre-)eclampsia, n (%)	23 (22)	26 (25)
Fetal distress, n (%)	23 (22)	15 (15)
IUGR, n (%)	16 (15)	19 (18)
Caesarean section, n (%)	48 (46)	38 (37)
5 min Apgar score, median (IQR)	9 (8-9)	8 (7-9)
Singletons, n (%)	36 (35)	47 (46)

Table 2. Secondary outcomes: BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; NEC = nectrotizing enterocolitis; ROP = retinopathy of prematurity; IVH = intraventricular hemorrhage; PVL = periventricular leucomalacia.

Secondary outcomes	EFURCI N = 104	Conventional N = 103	Univariate anaysis (P)	Odds Ratio (95% CI)
Intubation delivery room, n (%)	18 (17)	37 (36)	0.002	0.37 (0.20-0.70)
Total period of mechanical ventilation of intubated infants < 72 hours of age, days, median (IQR)	2.5 (1-8.3) N = 38	4.5 (2-11.5) N = 52	0.2	
Total period of NCPAP of total group, days, median (IQR)	2 (0.3-8)	2 (0-11)	0.04	
Surfactant doses, mean (SD)	0.4 (0.8)	0.6 (1.0)	0.3	
Surfactant > 1 dose, n (%)	10/104 (10)	22/103 (21)	0.02	0.39 (0.18-0.88)
Mortality, n (%)	2 (2)	4 (4)	0.4	
$BPD^{total,}$ n (%*)	22 (22*)	34 (34*)	0.05	
$BPD_{moderate\text{-}severe,}$ n (%*)	9 (9*)	19 (19*)	0.04	0.41 (CI 0.18-0.96)
PDA needing treatment, n (%)	21 (20)	16 (16)	0.4	
NEC ≥ stage 2, n (%)	0 (0)	1 (1)	0.5	
ROP >grade 3, n (%)	0 (0)	1 (1)	0.5	
IVH grade 3+4, n (%)	7 (7)	3 (3)	0.3	
Cystic PVL, n (%)	2 (2)	5 (5)	0.4	

* = percentage of survivors

days (IQR): 2.7 (0.5-10) vs 4.3 (0.5-20); P = .01). In the subgroup of infants ventilated within 72 hours of age, total time of ventilatory support (including nasal CPAP) was less in the EFURCI than in the conventional group (median days (IQR): 10 (4-19.5) vs 15 (5.6-36.3); P = .04). The first pH, $PaCO_2$ and FiO_2 upon arrival in the NICU and maximum of FiO_2 used were similar in both groups (pH 7.23 ± 0.1 in both groups; $PaCO_2$ 6.9 ± 1.4 vs 6.8 ± 1.6 kPa; FiO_2 0.32 ± 0.17 vs. 0.32 ± 0.19; maximum FiO_2 used 0.4 ± 0.25 vs. 0.36 ± 0.19). The incidence of RDS was less in the EFURCI-group compared to the conventional group (39 (38%) of 104 vs. 56 (54%) of 103; P = .015; OR 0.50 (95% CI 0.29-0.88)). The incidence of pneumothoraces was not significant different between the groups (1 (1%) of 104 vs. 7 (7%) of 103; P = .07; OR 0.13 (95% CI 0.02-1.10)).

Post-hoc analysis of gestational age subgroups (Fig 2) showed that the greatest effect was at 28-30 weeks' gestation (intubation < 72 hours: 16 (32%) of 50 vs 27 (59%) of 47; P = .01; OR 0.33 (95% CI 0.14-0.76). In the subgroup < 28 weeks' gestation, fewer infants were intubated in the delivery room (8 (40%) of 20 versus 15 (79%) of 19; P =.02; OR 0.18 (CI 0.04-0.74)), but there was no significant difference in intubation < 72 hours (13 (65%) of 20 vs 15 (79%) of 19; not significant).

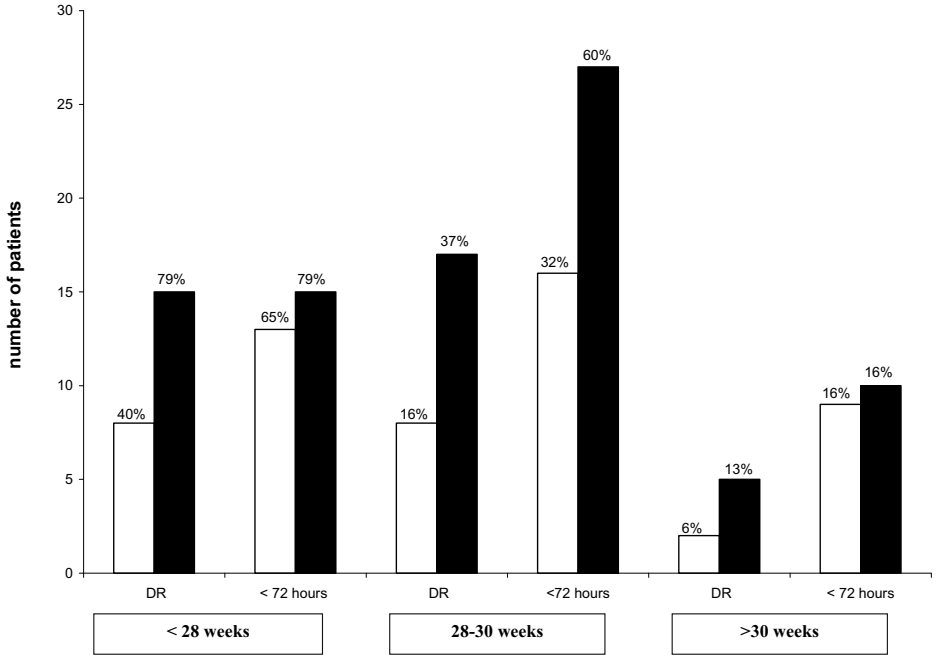

Figure 2. Number of infants intubated in delivery room and < 72 hours plotted against subgroups gestational age, EFURCI vs conventional.
White = EFURCI; black = conventional.

Discussion

This randomized controlled trial shows that very preterm infants need less intubation, mechanical ventilation, days on nasal CPAP and had less RDS, air leaks and moderate-to-severe BPD when a prolonged inflation through a nasopharyngeal tube, immediately followed by nasal CPAP (EFURCI), is used instead of bag and mask ventilation and nasal CPAP on admission to the NICU. Treatment with surfactant was not different but fewer infants received more than one dose in the EFURCI group. These data suggest that this lung recruitment maneuver (sustained inflation followed by nasal CPAP) is a more effective management strategy for ventilation of very preterm infants in the delivery room.

This is the first randomized controlled trial in which the EFURCI ventilation strategy is compared with bag and mask ventilation advised by international neonatal resuscitation guidelines (3). Our results are consistent with the findings in the retrospective report of Lindner et al., who compared the same lung recruitment manoeuvre and early nasal CPAP in

1996 with elective intubation as historical control in 1994 (10). Their study group consisted of smaller infants (mean gestational age 26.9 weeks and birthweight 739 grams in the intervention group), but their intubation rate in the delivery room decreased from 84% to 40% ($P < .001$) and 7% were never intubated in the 1994 group compared with 25% in 1996 ($P < .01$). The rate of moderate-to-severe BPD rate decreased from 32% to 12% ($P< 0.05$) (10). Consistent with our results, no harmful effects of their new approach were found; for example, no increased rates of IVH or pneumothorax.

Our trial showed that the EFURCI approach allows more infants to breathe during the first days with early nasal CPAP alone. Early nasal CPAP and selective surfactant treatment is an accepted alternative, and retrospective studies have shown less morbidity when early nasal CPAP is used in the delivery room to avoid intubation, even if CPAP fails later on and intubation follows (1;4;22-24). More prospective trials are under way, but there is currently insufficient information to evaluate the effectiveness of prophylactic (=early) nasal CPAP in very preterm infants (25). Finer et al. found, in a feasibility study among infants <28 weeks' gestation receiving CPAP/PEEP or not in the delivery room, no differences in intubation rate or surfactant use (26).

Animal studies have shown that an inflammatory process can be initiated with the first large manual breaths during resuscitation and may ultimately lead to BPD (5-9). Very preterm infants may not be able to generate high enough inspiratory pressures to achieve effective lung expansion and therefore need respiratory support (27;28). A prolonged inflation time, used if spontaneous breathing is inadequate, may help the preterm infant to overcome the long time constant of a liquid-filled lung and prevent the use of potentially dangerous, high inspiratory pressures (29;30).

The beneficial effects of a sustained inflation were not confirmed in recent randomized controlled trials (31;32). Lindner et al. compared a 15 seconds inflation to intermittent mandatory ventilation in infants <29 weeks' gestation. Consistent with our findings there was no difference regarding the intubation rate < 72 hours in this group of infants (31). Harling et al. used a different method by comparing a sustained inflation of 5 seconds with a conventional inflation of 2 seconds (32). Both studies lacked power because of small sample sizes. To maintain an adequate lung volume after inflation and to prevent atelectrauma, application of PEEP/CPAP is necessary (33-35). Starting time of early nasal CPAP is important, because a noncompliant, surfactant-deficient lung has a tendency to collapse and lung volume is not maintained if CPAP/PEEP is not given immediately to keep the lung open. Self-inflating bags may deliver insufficient or excessively high peak inspiratory pressure and minimal PEEP, leading to volutrauma and atelectrauma, even when a manometer is incorporated (14;18;19). A pressure-limited mechanical device with a T-piece delivers more consistent peak inspiratory pressure and PEEP and is better able to deliver

a sustained inflation compared to a self-inflating bag (13-16). Another advantage is that it is easy to use and thereby increases the chance of effective ventilation, even in the hands of inexperienced physicians (14). It is difficult to deliver PEEP with a face mask as the seal can break very easily (15;36). To avoid this PEEP leakage, a nasopharyngeal tube is used as interface. Data is limited, but a randomized trial showed significant less intubations in neonates with moderate asphyxia (17). Another advantage of using a nasopharyngeal tube as interface is that CPAP/PEEP can be continued very easily and directly after resuscitation.

There was a significant decrease of RDS in the EFURCI group. A possible explanation for this is that the EFURCI intervention was effective in preserving surfactant. During initial assessment of a very preterm infant in the delivery room it is difficult to differentiate between respiratory distress due to transitional problems or RDS and a trial of early nasal CPAP provides time to solve this problem. In the conventional group, some preterm neonates who were intubated and ventilated in the delivery room may have had transitional problems, but developed RDS secondary to lung injury.

Some very preterm infants failed early nasal CPAP later on, especially infants <28 weeks' gestation with RDS. The maximum level of CPAP used was 8 cm H_2O and a higher level of CPAP or a recruitment manoeuvre during CPAP might have reduced later treatment failure. Another explanation for early nasal CPAP failure may have been the low threshold for intubation and surfactant treatment at our institution (FiO_2 > 40% or $PaCO_2$ > 8.0 kPa). This low threshold was chosen to prevent the disadvantageous and deleterious effects of a late rescue with surfactant treatment (FiO_2 ≥0.6) in infants who are quickly deteriorating because of RDS (11;37). Prophylactic or early surfactant treatment of neonates requiring mechanical ventilation is more effective than late rescue treatment (38;39), but has the potential disadvantage that some preterm neonates are treated who are surfactant sufficient and will not develop RDS.

There are limitations of this randomized controlled trial. To reach the most effective application of an open lung strategy, we combined several techniques (mechanical pressure-limited device, prolonged inflation, nasopharyngeal tube as interface and direct nasal CPAP in the delivery room). This makes it impossible to determine which factor contributes most to the final result. In the conventional method a higher pressure is used initially to open the lung. Although this technique is in agreement with the international guidelines, this could have contributed to the poorer outcome. Biases in the management could have occurred as the study was not blinded and the staff performing the study also took care of the infants later on. However, the decision to intubate was made by clinicians other than the investigators. Whenever one of the investigators was supervising, one of their colleagues (fellow) made the decision to intubate or not in the infants included in the study. We tried to minimize these biases by maintaining strict criteria and definitions during the trial. This

trial was performed in a single center with experienced neonatologists, trained in the techniques of EFURCI, and it is possible that others might not get the same results.

Limits of viability in the Netherlands are set at 25 weeks' gestation, so the results of this study cannot be applied to infants < 25 weeks' gestation. We detected little effect of the EFURCI-approach in infants < 28 weeks' gestation, but this trial was not designed and powered to detect a difference in this subgroup. Whether the EFURCI approach is more efficient and less injurious among the most vulnerable preterm infants, that is, those with a gestational age of 23 to 27 weeks, needs further evaluation.

In conclusion, this randomized controlled trial comparing two ventilatory approaches has shown that the combination of a sustained inflation breath and early nasal CPAP supplied by a mechanical pressure-limited device and a nasopharyngeal tube as interface is a more efficient strategy than repeated manual inflations with a self-inflating bag and mask for the early respiratory management of very preterm infants in the delivery room. Early nasal CPAP also buys time to differentiate between RDS and transition problems and reduces the number of preterm infants intubated unnecessarily. More investigation is needed to determine which part of the EFURCI approach contributed the most. Although this trial has shown the importance of early respiratory management for pulmonary outcome (BPD) in preterm infants, more randomized trials, especially in infants < 28 weeks of gestation, are needed to develop an optimal strategy for extremely preterm infants.

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