Article

Choosing the optimal ventilatory support at birth for very preterm infants to prevent evolution to bronchopulmonary dysplasia

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Keywords

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Abstract

Bronchopulmonary dysplasia remains a severe complication of prematurity and invasive ventilation is a major risk factor for developing bronchopulmonary dysplasia. Our aim is to compare different ventilation methods in the delivery room and the subsequent risk of bronchopulmonary dysplasia. Medline database was searched from 2005 to 2019. Articles in English including infants born at ≤ 32 weeks who received non-invasive respiratory support in the delivery room were considered. Sixteen articles were included. A systematic review and meta-analysis found a reduction of bronchopulmonary dysplasia in very preterm infants treated with nasal continuous positive airway pressure. Pooled analysis found a significant reduction in the combined outcome of bronchopulmonary dysplasia or death or both at 36 weeks in infants randomized to the nasal continuous positive airway pressure group, number needed to treat of 25. Another meta-analysis found a significant lower risk on death or bronchopulmonary dysplasia using strategies avoiding mechanical ventilation (P=0.008), number needed to treat of 32. Only one study, a cohort study with a historical control group, found a statistically significant lower occurrence of bronchopulmonary dysplasia in very preterm infants who received sustained lung inflations.

Conclusion: prevention of bronchopulmonary dysplasia in very and extremely preterm infants should start in the delivery room. The use of early nasal continuous positive airway pressure could be recommended. Sustained inflations and nasal intermittent positive pressure ventilation in the delivery room do not reduce the incidence of bronchopulmonary dysplasia and are not recommended.

Introduction

The number of very preterm infants (infants born at 28 - 32 weeks) and extremely preterm infants (infants born < 28 weeks) is increasing every year (1). Many of these infants have functional and structural immaturity of the lung needing respiratory support at birth. Despite the use of surfactant replacement therapy, antenatal and postnatal corticosteroids and non-invasive ventilation bronchopulmonary dysplasia (BPD) remains a major cause of morbidity and mortality in very and extremely preterm infants. The overall incidence of BPD in infants born ≤ 32 weeks is around 45% (2). Non-invasive ventilatory support started in the delivery room instead of intubation and mechanical ventilation is thought to reduce the rate of BPD and death (2).

BPD or neonatal chronic lung disease (CLD) is a major complication of prematurity. BPD is most often defined as the need for supplemental oxygen at 36 weeks postmenstrual age (2). BPD can be mild, moderate or severe and is categorized by the respiratory support method used at 36 weeks postmenstrual age: grade 1 BPD, infants receiving nasal cannula ≤ 2 L/min, grade 2 BPD, infants receiving nasal cannula > 2 L/min or non-invasive positive airway pressure, grade 3 BPD, infants receiving mechanical ventilation (3). The pathogenesis of BPD is multifactorial (2). The structural complexity of the lung is lost, causing reduced alveolar development with loss of surface area for gas exchange. Genetic susceptibility and hereditary influences on the expression of genes important for the synthesis of surfactant, regulation of inflammation and development of blood vessels play a role in the development of BPD. Various prenatal exposures (intrauterine growth restriction, chorioamnionitis,…) can make the lungs more susceptible for injury (4). The more premature the infant and the lower the birth weight, the higher the risk of BPD. Since invasive ventilation is also an important risk factor for developing BPD in preterm infants, the use of non-invasive ventilation is an important way of preventing BPD (1).

There are various non-invasive ventilatory support strategies that can be started in the delivery room. Continuous positive airway pressure (CPAP) ensures stabilization of the upper airways and chest wall, improves functional residual capacity, tidal volume and oxygenation and ensures less work of breathing, apneas and lung resistance (1). Nasal intermittent positive pressure ventilation (NIPPV) is another form of non-invasive respiratory support. NIPPV can reduce work of breathing and the risk of BPD (1). Sustained lung inflation (SLI) is a positive pressure inflation that is used to establish an increase in functional residual capacity. The inflation times range between 5 and 15 seconds. SLI provides early functional residual capacity, augments lung aeration and facilitates transition at birth. Many different interfaces for delivery of non-invasive ventilatory support can be used. It is unknown what the best delivery method is (5,6).

By far there has been little clinical comparison on the risk of BPD in infants ≤ 32 weeks between the different ventilatory support modes used immediately after birth, in the delivery room. This review compares different modes of ventilatory support used in infants ≤ 32 weeks who need support in the delivery room and their risk of BPD and may thus guide clinical practice.

Methods

Search strategy

We searched and analyzed the Medline database to identify all relevant published articles starting from 2005 up to and including 2019. This period was chosen arbitrarily. We used the Pubmed advanced search builder. We used the following search terms ‘Respiratory support at birth’ AND ‘Preterm infants’, ‘Ventilatory support at birth’ AND ‘Preterm infants’, ‘Nasal CPAP at birth’ AND ‘Preterm infants’, (((intubation) OR resuscitation) OR nasal CPAP) OR positive pressure ventilation AND preterm infants AND ((bronchopulmonary dysplasia) OR chronic lung disease) OR mechanical ventilation AND (("2005"[Date - Publication] : "2019"[Date - Publication])), (respiratory support at birth) OR ventilatory support at birth AND preterm infants AND ((bronchopulmonary dysplasia) OR chronic lung disease) OR mechanical ventilation AND ("2005"[Date - Publication] : "2019"[Date - Publication])

Inclusion criteria

All relevant articles from 2005 up to and including 2019 published in English were included in this review. Older articles and articles in other languages were excluded. We selected articles based on title and abstract containing BPD or CLD as primary or secondary outcome. In the second search the references of the articles included in the first search were read. Articles from before 2005 were also included in the second search. Various types of studies were considered for this review.

Type of participants

Studies whose study population consists of infants born at ≤ 32 weeks of gestational age, were included in this review.

Type of interventions

Different types of interventions were eligible for inclusion. Nasal continuous positive airway pressure (nCPAP), positive pressure ventilation (PPV), NIPPV, administered through an interface for delivery of non-invasive ventilatory support. For inclusion, the intervention had to start in the delivery room, immediately after birth.

Outcomes

All articles with BPD or CLD as primary or secondary outcome were included. BPD is defined as the need for supplemental oxygen at 36 weeks postmenstrual age or 28 days after birth.

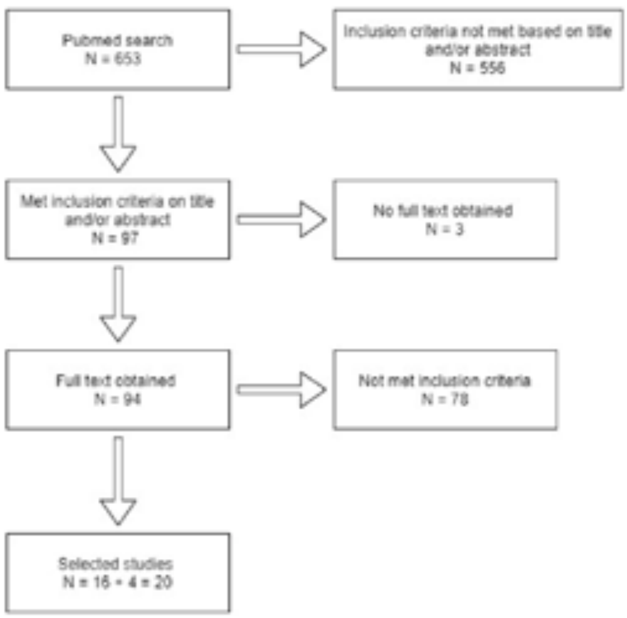
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was not used because this review is not a systematic review or meta-analysis and no statistical analysis was performed.

Results

Results of the literature search

The Pubmed search led to 653 articles. Of these articles, 556 did not meet the inclusion criteria based on title and/or abstract. Of 3 articles no full text could be obtained. Ninety-four articles were completely read. Of these 94 articles, 78 did not meet the inclusion criteria. These articles were excluded based on study population (preterm infants > 33 weeks of gestational age), type of intervention, BPD not as primary or secondary outcome and intervention not started in the delivery room, immediately after birth. Twenty articles were included in this review. Four articles were added after the initial search based on the references of the initial 16 articles. Of these twenty articles, seven are randomized controlled trials (RCT), two systematic reviews and meta-analysis, one meta-analysis, four retrospective studies, two cohort study and one policy statement (Figure 1).

Figure 1 : *Flowchart of the literature search. N, number*



Nasal CPAP

The characteristics of the studies on nCPAP are summarized in table 1.

Morley et al. conducted a RCT to investigate whether nCPAP at a pressure of 8 cm H2O compared to intubation would reduce the rate of death or BPD in very preterm infants (7). A total of 610 infants between 25 and 28 weeks of gestational age were randomized. There was a lower risk of the combined outcome of death or the need for oxygen therapy at 28 days after birth in the CPAP group (odds ratio 0.63; 95% confidence interval (CI) 0.46-0.88; P=0.006). There was no statistically significant difference in the rate of death or BPD at 36 weeks gestational age, 33.9% in the CPAP group and 38.9% in the intubation group (odds ratio 0.80; 95% CI 0.58-1.12; P=0.19).

In the RCT of Badiee et al. 72 preterm infants were randomized to either very early CPAP initiated at 5 minutes after birth or late CPAP initiated 30 minutes after birth (8). Infants in the very early CPAP group received continuous distending pressure of 6 cm H2O through a nasopharyngeal tube. The infants allocated to the late CPAP group received initial oxygen through an oxygen hood until 30 minutes after birth. Then they received CPAP at a pressure of 6 cm H2O through a nasopharyngeal tube. No statistically significant differences in BPD between the two groups was found (P=0.5). In the very early CPAP group BPD occurred in 2.8% and in the late CPAP group in 5.6%.

A retrospective study carried out by Mehler et al. evaluated 164 extremely low gestational age newborn infants under 26 weeks (9). These infants were treated with CPAP via face mask, fraction of inspired oxygen (FiO2) 0.6 and positive end-expiratory pressure (PEEP) of 8 cm H2O. Surfactant through an endotracheal catheter was administered if necessary. The outcomes of these infants were compared to 44 extremely low gestational age infants in the control group. Infants in the control group who were not breathing at birth received PPV with FiO2 0.6. The infants who were breathing were stabilized with CPAP. The incidence of BPD in the study group was significantly lower (18% vs. 37%, P<0.05).

Schmölzer et al. conducted a systematic review and meta-analysis (10). Four RCTs were included. In total 2782 infants < 32 weeks were randomized to either nCPAP or intubation at birth. There was a reduction of BPD with borderline statistical significance in favor of the nCPAP group (risk ratio 0.91; 95% CI 0.82-1.01). A pooled analysis was conducted. This demonstrates a significant reduction in the combined outcome of BPD or death or both at 36 weeks corrected gestational age for infants randomized to the nCPAP group (risk ratio 0.91; 95% CI 0.84-0.99). Twenty-five infants need to be treated in the delivery room with nCPAP to prevent one additional infant from having BPD at 36 weeks of gestational age.

Fischer et al. conducted a meta-analysis that compared non-invasive respiratory strategies with mechanical ventilation (11). Different methods of nCPAP with or without surfactant administration were compared with endotracheal mechanical ventilation or intubation, surfactant and extubation (INSURE). Nine RCTs of 3486 infants were included in this meta-analysis. The risk of death or BPD significantly decreased by using strategies to avoid mechanical ventilation (risk ratio 0.90; 95% CI 0.84-0.97; P=0.008), number needed to treat of 32. There was no significant effect of avoiding mechanical ventilation on death (risk ratio 0.88; 95% CI 0.73-1.06; P=0.18) or BPD alone (risk ratio 0.92; 95% CI 0.83-1.01; P=0.09).

The retrospective study of Miksch et al. compared the effect of early nCPAP use to a historical control group (12). They found a statistically significant difference between both groups: 24% of the infants in the control group and 8% of the infants in the intervention group had BPD at 36 weeks of postmenstrual age (P=0.003). Gittermann et al. however found no statistically significant difference in the prevalence of BPD after the introduction of early nCPAP (P=0.94) (13). In the study of De Klerk et al. the introduction of early nCPAP did not change the number of infants needing respiratory support at 36 weeks of gestational age, compared to a historical cohort (14).

Since 2014, the American Academy of Pediatrics recommends the use of CPAP immediately after birth followed by selective surfactant administration as an alternative to intubation with prophylactic or early surfactant administration (15).

Table 1 Characteristics of the studies on nCPAP

Study	Study population	Intervention	Outcome (BPD)	BPD definition
Morley et al., 2008 (7) RCT	n = 610 GA 25+0–28+6	CPAP vs. intubation	Death or BPD at 36 weeks: 33.9% CPAP group 38.9% intubation group Odds ratio 0.80; 95% CI 0.58-1.12; P=0.19 Death or oxygen therapy at 28 days: odds ratio 0.63; 95% CI 0.45-0.88; P=0.006	Need for oxygen at 36 weeks corrected gestational age Need for oxygen at 28 days
Badiee et al., 2012 (8) RCT	n = 72 GA 25–30	Very early CPAP vs. late CPAP	2.8% very early CPAP 5.6% late CPAP P=0.5	Need for oxygen at 28 days
Mehler et al., 2012 (9) Retrospective study	n = 164 (study group) GA < 26 n = 44 (control group) GA < 26	CPAP vs. PPV	18% CPAP group 37% PPV group P<0.05	Need for oxygen at 36 weeks corrected gestational age
Schmölzer et al., 2013 (10) Systematic review + meta-analysis	n = 2782 GA < 32	nCPAP vs. intubation	BPD: risk ratio 0.91; 95% CI 0.82-1.01 BPD or death, or both (pooled analysis): risk ratio 0.91; 95% CI 0.84-0.99; NNT = 25	Need for oxygen at 36 weeks corrected gestational age
Fischer et al., 2018 (11) Meta-analysis	n = 3486 GA 23+0–29+6	nCPAP vs. mechanical ventilation	Death or BPD: risk ratio 0.90; 95% CI 0.84-0.97; P=0.008; NNT = 32	Need for oxygen at 36 weeks corrected gestational age
Miksch et al., 2008 (12) Retrospective study	n = 93 (study group) n = 63 (control group) GA < 32	nCPAP vs. IPPV or intubation	8% study group 24% control group P=0.003	Need for oxygen at 36 weeks corrected gestational age
Gittermann et al., 1997 (13) Retrospective study	n = 70 (study group) n = 57 (control group) GA 28+0-32+0	Early nCPAP vs. other ventilatory support methods	30% study group 32% control group P=0.94	Need for oxygen at 28 days
De Klerk et al., 2001 (14) Retrospective study	n = 59 (study group) n = 57 (control group) GA < 35	Early nCPAP vs. nCPAP or oxygen without positive pressure or intubation and IMV	BPD: 0% study group, 6% control group; P=0.22 Death or BPD: 3% study group, 11% control group; P=0.25	Need for oxygen at 36 weeks corrected gestational age

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; IMV, intermittent mandatory ventilation; vs., versus; GA, gestational age; RCT, randomized controlled trial; NNT, number needed to treat; CI, confidence interval

Table 2 Characteristics of the studies on SLI

Study	Study population	Intervention	Outcome (BPD)	BPD definition
Te Pas et al., 2007 (16) RCT	n = 207 GA 25–32	SI + nCPAP (EFURCI group) vs. manual inflations + nCPAP (conventional group)	BPD moderate – severe: 9% EFURCI group vs. 19% conventional group P=0.04	Need for oxygen at 36 weeks corrected gestational age
Lista et al., 2015 (17) RCT	n = 291 GA 25+0–28+6	SLI + nCPAP vs. nCPAP alone	38.5% SLI group 35% nCPAP group unadjusted odds ratio 1.17; 95% CI 0.80-1.71; P=0.42	Need for oxygen at 36 weeks corrected gestational age
Jiravisitkul et al., 2016 (18) RCT	n = 81 GA 25–32	SLI vs. PPV	10% SLI group 22% non-SLI group P=0.15	Moderate BPD: need for <30% oxygen at 36 weeks Severe BPD: need for ≥30% oxygen at 36 weeks
Ngan et al., 2017 (19) RCT	n = 162 GA 23+0–32+6	SI-guided exhaled carbon dioxide vs. PPV	23% SI group 33% PPV group P=0.09	Need for oxygen at 36 weeks corrected gestational age
Kirpalani et al., 2019 (20) RCT	n = 426 GA 23+0–26+6	SI vs. IPPV	42.8% SI group 43.6% IPPV group risk ratio 1.0; 95% CI 0.8-1.2; P=0.92	Need for oxygen at 36 weeks corrected gestational age
Lindner et al., 1999 (21) Retrospective cohort study	n = 123 GA < 29	MV (1994) vs. SLI (1996)	32% MV group 12% SLI group P<0.05	Need for oxygen at 36 weeks corrected gestational age
Lista et al., 2010 (22) Cohort study	n = 208 GA < 32	SLI vs. PEEP	7% SLI group 25% control group P=0.004	Need for oxygen at 36 weeks corrected gestational age
Schmölzer et al., 2015 (23) Systematic review + meta-analysis	n = 611 GA < 33	SLI vs. IPPV	BPD: risk ratio 0.84	Need for oxygen at 36 weeks corrected gestational age
Fischer et al., 2018 (11) Meta-analysis	n = 854 GA 23+0–32+6	SI vs. IPPV	BPD: risk ratio 0.78; 95% CI 0.57-1.05; P=0.10 BPD or death: risk ratio 0.85; 95% CI 0.65-1.12; P=0.25	Need for oxygen at 36 weeks corrected gestational age

BPD, bronchopulmonary dysplasia; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; IPPV, intermittent positive pressure ventilation; SI, sustained inflation; SLI, sustained lung inflation; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; EFURCI, early functional residual capacity intervention; vs., versus; GA, gestational age; RCT, randomized controlled trial; CI, confidence interval

Sustained lung inflation

The characteristics of the studies on SLI are summarized in table 2.

Te Pas et al. compared a sustained inflation (SI) through a nasopharyngeal tube followed by early CPAP or repeated manual inflations through a self-inflating bag and mask if necessary followed by nCPAP (16). A total of 207 very preterm infants, 25-32 weeks of gestational age, were randomized. Very preterm infants in the early functional residual capacity intervention (EFURCI) group received a SI of 20 cm H2O for 10 seconds through a nasopharyngeal tube and T-piece ventilator. This could be repeated with a pressure of 25 cm H2O if breathing remained insufficient. After this early nCPAP at 5-6 cm H2O was initiated. Infants randomized to the conventional intervention group received initial inflation pressures of 30-40 cm H2O during 30 seconds. They only received nCPAP in the neonatal intensive care unit if necessary. Very preterm infants in the EFURCI group developed less moderate-severe BPD compared with very preterm infants in the conventional group (9% vs. 19%, P=0.04). There was also a lower rate of BPD (22% vs. 34%, P=0.05) in infants receiving SI followed by nCPAP.

Lista et al. conducted a RCT to compare prophylactic SLI (25 cm H2O for 15 seconds) followed by nCPAP at 5 cm H2O with CPAP alone at birth (17). Infants born at 25 weeks to 286/7 weeks were randomly assigned to one of these two groups. The secondary outcome was BPD. The overall incidence of BPD in the SLI group was 38.5% and in the nCPAP group 35% (unadjusted odds ratio 1.17; 95% CI 0.80-1.71; P=0.42). In infants surviving at 36 weeks the rate of BPD was 54.8% in the SLI group and 53.2% in the nCPAP group.

Jiravisitkul et al. conducted a RCT which compared SLI with standard resuscitation in very preterm infants (25-32 weeks GA) (18). Eighty-one infants were included. Very preterm infants allocated to the SLI group received a pressure-controlled inflation of 25 cm H2O for 15 seconds using a mask via a T-piece resuscitator. This was followed by CPAP at 6 cm H2O via face mask for 5-10 seconds. Very preterm infants in the non-SLI group received PPV with peak inspiratory pressure (PIP) of 15-20 cm H2O and PEEP of 5 cm H2O for 30 seconds via a T-piece resuscitator. In this RCT no difference in the incidence of BPD between the groups was observed (10% SLI group, 22% non-SLI group, P=0.15).

In the RCT of Ngan et al. infants ≤ 32 weeks were randomized to a SI guided by exhaled carbon dioxide (ECO2) or to mask PPV with a PIP of 24 cm H2O (19). Infants randomized to the SI group received an initial SI with a PIP of 24 cm H2O over 20 seconds. The second SI depended on the amount of ECO2. When the ECO2 was ≤ 20 mm Hg the second SI was 20s. When the ECO2 was > 20 mm Hg the second SI lasted 10s. Both groups had similar rates of BPD (SI group 23%, PPV group 33%, P=0.09).

The SAIL randomized clinical trial by Kirpalani et al. randomly assigned extremely preterm infants from 23 to 26 weeks to either intermittent positive pressure ventilation (IPPV) or SI (20). A total of 426 infants completed the trial. Infants randomized to the SI group received an initial SI at a pressure of 20 cm H2O for 15 seconds. A second SI at a peak pressure of 25 cm H2O for 15 seconds was given if necessary. Infants in the standard resuscitation group received IPPV with PEEP. The rate of BPD in the SI group was 42.8% vs 43.6% in the resuscitation group (risk ratio 1.0; 95% CI 0.8-1.2; P=0.92). SI compared with IPPV did not reduce the risk of BPD. The study was closed early because of an excess mortality rate with SI in the first 48 hours and may therefore be underpowered.

Lindner et al. performed a retrospective cohort study. Between 1994 and 1996 there was a change of delivery room management. In 1994 the infants received an inflation using a flow-inflating bag followed by mechanical ventilation or endotracheal intubation. In 1996, 67 infants < 29 weeks in the delivery room received a SI of 20 cm H2O for 15 seconds using a nasopharyngeal tube. The SI could be repeated a second time with a pressure of 25 cm H2O if required. This was followed by CPAP. If necessary these infants received mechanical ventilation. In 1994, 13 infants (32%) developed BPD compared with 6 infants (12%) in 1996 (P<0.05) (21).

Lista et al. conducted a cohort study with a historical control group (22). A total of 208 infants < 32 weeks of gestational age were included. The infants enrolled in the intervention group (SLI group) were studied prospectively and the infants in the control group were studied retrospectively. Eighty-nine infants in the SLI group received an initial SLI of 25 cm H2O using a mask and T-piece ventilator for 15 seconds. This was followed by delivery of 5 cm H2O PEEP. If breathing remained insufficient this could be repeated a second time. Hundred and nineteen infants were enrolled in the control group. They received 5 cm H2O PEEP after birth. After the initial ventilation both groups received nCPAP of 5 cm H2O or IPPV with a PIP < 25 cm H2O. A significant lower occurrence of BPD was found in the SLI group (7% vs. 25%, P=0.004).

A systematic review and meta-analysis was conducted by Schmölzer et al. (23). SI during resuscitation at birth was compared with IPPV. Four trials with a total of 611 infants < 33 weeks of gestational age were included in the analysis. No significant difference in BPD, death or the combined outcome of BPD and death could be found.

Another meta-analysis was conducted by Fischer et al. where SI was compared with IPPV (11). In this meta-analysis six RCTs were included. A total of 854 infants < 33 weeks of gestational were studied. The infants in the SI group received 1-3 sustained inflations for 5-20 seconds with a pressure of 20-30 cm H2O. No effect could be found of SI on death, BPD or the combined outcome of death or BPD (BPD: risk ratio 0.78; 95% CI 0.57-1.05; P=0.10; death: risk ratio 1.31; 95% CI 0.80-2.14; P=0.29; combined outcome: risk ratio 0.85; 95% CI 0.65-1.12; P=0.25).

NIPPV

A retrospective study was performed by Biniwale et al. The impact of non-invasive ventilation using NIPPV for resuscitation in very low birth weight infants was evaluated. A total of 221 very low birth weight infants < 32 weeks were included. One hundred nineteen infants received NIPPV and were compared to a historical control group of 102 infants who received PPV through a face mask. The infants had a mean gestational age of 27 weeks in the NIPPV group and 27.1 weeks in the face mask group. The intubation rates in the NIPPV group in the delivery room were significantly lower than in the face mask group (31% vs. 85%; P<0.001). No significant differences in the rates of BPD between both groups could be found (37% (face mask group) vs. 39% (NIPPV group); P=0.88) (24).

Discussion

Effect of nCPAP on BPD

Two meta-analyses and a RCT compared nCPAP with intubation immediately after birth (7,10,11). CPAP aims to avoid immediate intubation and thus additional lung damage after birth. While there are clear advantages in the short term, the effect on BPD is not as clear. The RCT only found a trend towards less death or BPD at 36 weeks postmenstrual age, the first meta-analysis a borderline statistically significant effect and the second meta-analysis only a statistically significant effect on the combined outcome of death or BPD, not on BPD alone (7,10,11).

There are several limitations to these studies. None of the four RCTs in the meta-analysis of Schmölzer et al. were blinded (thereby increasing the chance of bias) and the studies were performed when there was no consensus on the oxygen concentration initially used during neonatal resuscitation (10). In the RCTs that applied less invasive surfactant administration or minimally invasive surfactant therapy, intervention could take place within 2 hours after birth, possibly outside the delivery room (11).

Only one study found a statistically significant difference on BPD at 36 weeks postmenstrual age by introducing the use of early nCPAP (12). While nCPAP still seems to be the best way to prevent BPD in the delivery room, the exact settings for an optimal effect are not clear yet. Badiee et al. found no statistically significant difference between infants receiving CPAP at 5 minutes vs. 30 minutes after birth (8). Early use of nCPAP could reduce the incidence of atelectasis by increasing functional residual capacity during expiration and improves oxygenation and lung compliance. The role of the devices that are used to provide nCPAP is also not clear, neither is the optimal amount of FiO2. Finally, a lot of other delivery room protocol interventions like delayed cord clamping, the application of surfactant etc. can influence the results.

Effect of SLI on BPD

Based on the reviewed studies (Table 2) there is no evidence that the use of SI in the delivery room could reduce the incidence of BPD and it is therefore not recommended. These studies also have their limitations however, the most important of which we will discuss here.

The systematic review of Schmölzer et al. found no significant difference in BPD, death or the combined outcome of BPD and death in infants receiving SI after birth (23). The four RCTs included in this analysis used different oxygen concentrations (from 21% to 100%). Only one study included infants < 25 weeks of gestational age. These infants have the highest risk of needing intubation immediately after birth. Different ventilation devices were used to deliver SI or IPPV. The SAIL randomized clinical trial and the RCT of Ngan et al. were both underpowered (19,20). Different aspects of delivery room care changed over time (use of a nasopharyngeal tube and a mechanical ventilator, positive pressure ventilation and sustained inflations). In the meta-analysis of Fischer et al. different definitions of BPD were used in the included RCTs (11). They remark that the lack of effect may possibly be due to too high pressure and too long duration of SI or due to inefficient SI in infants with apnea at birth.

Only three studies found a statistically significant reduction of BPD by SI, but also here important limitations play a role.

The RCT conducted by Te Pas et al. found a significant reduction in the rate of moderate-severe BPD in infants in the EFURCI group, but this intervention not only included a SI, but also PEEP through a T-piece ventilator (whereas the control group received repeated manual inflations through a self-inflating bag and mask with only minimal PEEP) (16). They also found less BPD in infants receiving a SI followed by nCPAP. In this study there are more delivery room changes than just a SI. Prolonged inflations, use of a nasopharyngeal tube as interface, the delivery of PEEP and nCPAP in the delivery room could have contributed to the lower rate of BPD. Because various aspects of delivery room care have changed over time, it is difficult to determine how much difference (if any) can be attributed to SI.

The cohort study of Lista et al. found a statistically significant lower incidence of BPD in the SLI group (22). A historical control group constitutes a bias because over time various changes took place in the care for preterm infants. Another limitation could be the use of a neonatal mask instead of a nasopharyngeal tube which could be more efficient in preventing PEEP leakage.

In the retrospective cohort study (with small sample size) of Lindner et al. there was a statistically significant difference of BPD in the early low birth weight infants born in 1996 (21). This can be attributed to various factors such as the use of higher doses of prenatal betamethasone, more infants with intrauterine growth retardation and the use of CPAP after SI in the delivery room.

Effect of NIPPV on BPD

The retrospective study of Biniwale et al. showed a decrease in intubation and invasive ventilation rates, but no significant difference in the incidence of BPD between both groups could be found. The use of a nasal interface lowers the intubation rates in the delivery room, but has no effect on the incidence of BPD. Further studies are needed to compare NIPPV with nCPAP in the delivery room (24).

Ventilation devices and interfaces used in the delivery room

Different ventilation devices can be used in the delivery room such as self-inflating bags, flow-inflating bags and T-piece devices. Currently there is not enough evidence to guide clinicians' choice of ventilation device used during delivery room respiratory support. A self-inflating bag cannot provide PEEP or CPAP. A flow-inflating bag provides PEEP that is operator-depended and variable. T-piece devices deliver a predetermined level of PEEP and PIP. These three can all be used for mask ventilation. A T-piece device is most accurate to deliver a SI. Face masks and nasal prongs are interfaces used in the delivery room. A single nasal prong can reduce airway obstruction by the tongue, but air leak through the mouth and contralateral nostril can occur. Double nasal prongs can effectively be used to deliver PEEP and CPAP after birth. There are several factors that can affect mask ventilation and reduce its effectiveness: improper seal of the mask to the neonate's face which may cause leakage or airway obstruction, movements of the neonate and procedures such as repositioning the neonate (25,26). There are also several reflexes that can be induced by applying non-invasive ventilation during delivery room stabilization of preterm infants. Some of these reflexes, such as the trigeminocardiac reflex and the laryngeal chemoreflex, can compromise breathing. Consideration must be given to which device and interface can best be used during delivery room stabilization of preterm infants (27).

Conclusion

Lung-protective strategies should start immediately at birth, in the delivery room. The lungs of very preterm infants are susceptible to injury because of functional and structural immaturity of the lungs, no support by a stiff chest wall and surfactant deficiency. Most very and extremely preterm infants need respiratory support in the delivery room. Starting nCPAP in the delivery room in very preterm infants seems to result in a lower incidence of death and BPD at 36 weeks of gestational age. There is no evidence that the use of SI in the delivery room could reduce the incidence of BPD and SI is therefore not recommended as initial non-invasive respiratory support method. Before NIPPV can be implemented in the delivery room, more studies are needed.

Further studies are also needed to answer the following questions. How early should nCPAP be initiated after birth? Which type of interface, face mask, nasal mask or nasal prongs, could best be used to deliver nCPAP? Should different ventilation methods or interfaces be used in the delivery room depending on gestational age?

Conflict of interest: The authors declare that they have no conflict of interest.

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