

Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia: A Meta-analysis

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KEY WORDS

respiratory distress syndrome, bronchopulmonary dysplasia, newborn, mechanical ventilation, surfactant

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
 CENTRAL—Cochrane Central Register of Controlled Trials
 CI—confidence interval
 CNRN—Colombian Neonatal Research Network
 eMV—endotracheal mechanical ventilation
 FiO₂—fraction of inspired oxygen
 GA—gestational age
 INSURE—intubation, surfactant, extubation
 IVH—intraventricular hemorrhage
 nCPAP—nasal continuous positive airway pressure
 nHFOV—nasal high frequency oscillatory ventilation
 NICHD—National Institute of Child Health and Human Development
 nIPPV—nasal intermittent positive pressure ventilation
 NNT—number needed to treat
 RCT—randomized controlled trial
 RDS—respiratory distress syndrome

Drs Fischer and Bührer developed the concept and design of the study; they independently searched for relevant studies and extracted, assessed, and analyzed the data; Dr Fischer drafted the manuscript; Dr Bührer critically reviewed and revised the manuscript; and both authors approved the final manuscript as submitted.

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abstract



BACKGROUND AND OBJECTIVE: Mechanical ventilation via an endotracheal tube is a risk factor for bronchopulmonary dysplasia (BPD), one of the most common morbidities of very preterm infants. Our objective was to investigate the effect that strategies to avoid endotracheal mechanical ventilation (eMV) have on the incidence of BPD in preterm infants <30 weeks' gestational age (GA).

METHODS: In February 2013, we searched the databases Medline, Embase, and the Cochrane Central Register of Controlled Trials. Study selection criteria included randomized controlled trials published in peer-reviewed journals since the year 2000 that compared preterm infants <30 weeks' GA treated by using a strategy aimed at avoiding eMV with a control group in which mechanical ventilation via an endotracheal tube was performed at an earlier stage. Data were extracted and analyzed by using the standard methods of the Cochrane Neonatal Review Group. The authors independently assessed study eligibility and risk of bias, extracted data and calculated odds ratios and 95% confidence intervals, employing RevMan version 5.1.6.

RESULTS: We identified 7 trials that included a total of 3289 infants. The combined odds ratio (95% confidence interval) of death or BPD was 0.83 (0.71–0.96). The number needed to treat was 35. The study results were remarkably homogeneous. Avoiding eMV had no influence on the incidence of severe intraventricular hemorrhage.

CONCLUSIONS: Strategies aimed at avoiding eMV in infants <30 weeks' GA have a small but significant beneficial impact on preventing BPD. *Pediatrics* 2013;132:e1351–e1360

Bronchopulmonary dysplasia (BPD) was first described by Northway et al¹ as a pulmonary sequela of prolonged artificial ventilation and oxygen treatment in 32 neonates treated for severe respiratory distress syndrome (RDS). Affected infants had a prolonged clinical course of their lung disease, characteristic radiologic features, and a high mortality. Since that time, antenatal steroids,² exogenous surfactant treatment,³ gentler ventilation strategies,^{4,5} and other advances in neonatal intensive care have increased the survival of very premature infants and have reduced the rate of BPD.⁶ Although only a small number of preterm infants reveal the classic clinical course of BPD today, a recent study revealed a considerable BPD incidence of 42% in a large cohort of infants with gestational ages (GAs) of 22⁰/₇ to 28⁶/₇ weeks⁷ as defined by oxygen use at 36 weeks' postmenstrual age.⁸ This was attributed to a subset of infants who had an atypical pattern of chronic lung disease that was marked by delayed deterioration of pulmonary gas exchange in the absence of initial respiratory distress or only after clinical symptoms and radiologic signs of RDS had resolved.^{9,10} This so-called "new BPD"¹¹ is characterized by a milder clinical course and a maturational arrest of extremely immature lungs, and even occurs in the absence of marked hyperoxia and high ventilation settings.¹² Cohort studies suggest that avoiding endotracheal mechanical ventilation (eMV) and stabilizing very premature infants on early nasal continuous positive airway pressure (nCPAP) in the delivery room may be one way of reducing the new BPD.^{5,7} Randomized controlled trials (RCTs) have revealed that postnatal nCPAP is feasible and safe in premature infants between 24⁰/₇ and 28⁶/₇ weeks' GA, but they have not reported a significant reduction in BPD.^{13–16} New techniques to apply surfactant via a thin endotracheal catheter combine nCPAP

and endotracheal surfactant instillation without any need for eMV,^{17,18} and a recently published RCT revealed that this technique reduced moderate to severe BPD in a subgroup analysis of infants ≤ 28 weeks' GA.¹⁹

Presumably, avoiding endotracheal ventilation prevents volutrauma and thereby attenuates direct lung injury and the subsequent activation of the inflammatory process in the lung that precedes BPD.^{20,21} Although there is a consensus that gentle ventilation strategies, including nCPAP, have been effective in reducing the incidence of classic BPD,^{4,11} it is still unclear what the best strategy is for preventing BPD in premature infants < 30 weeks' GA. To date, several RCTs have compared "invasive" approaches to postnatal respiratory care with approaches designed to avoid eMV in this GA group. Therefore, the aim of the current study was to conduct a meta-analysis investigating the effect that avoiding eMV has on the incidence of BPD in premature infants < 30 weeks' GA.

METHODS

Criteria for Considering Studies for This Review

Randomized controlled clinical trials investigating strategies for avoiding eMV in preterm neonates < 30 weeks' GA were eligible for the meta-analysis. RCTs including more mature infants were eligible if $> 50\%$ of the study patients were < 30 weeks' GA and if the study authors provided stratified data for these infants. For trials to be included, they had to compare an intervention that avoided eMV (eg, nCPAP) with a control group in which mechanical ventilation by an endotracheal tube was performed at an earlier stage (eg, prophylactic mechanical ventilation or intubation, surfactant, extubation [INSURE]). The study design had to prescribe randomization within 24 hours after birth. Only studies published in full in peer-reviewed journals

were accepted. No language restrictions applied. We included studies published in 2000 and thereafter because they were considered to better reflect current practice, especially with regard to the use of antenatal steroids.²²

Types of Outcome Measures

The primary outcome was death or BPD at 36 weeks' GA. BPD was defined as the need for oxygen treatment at 36 weeks' GA, which corresponds to moderate to severe BPD under the National Institute of Child Health and Human Development (NICHD) workshop consensus definition.⁸ If the study authors did not provide clinical data about oxygen treatment at 36 weeks' GA, but did prescribe a standardized room air challenge to define oxygen requirement, data based on this physiologic definition of BPD²³ were accepted. As a secondary outcome, the incidence of severe intraventricular hemorrhage (IVH) was investigated. Severe IVH was defined as IVH grade 3 or 4.²⁴

Search Methods for Identification of Studies

The standard search methods of the Cochrane Collaboration were used.²⁵ The authors independently searched the databases Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), starting from January 2000 and continuing up to the last access on February 24, 2013. This search was combined with cross-referencing of previous reviews and trials, the use of information from experts, and occasional access to newer kinds of resources such as clinicaltrials.gov. A highly sensitive search strategy was used, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions, and followed specific recommendations for identifying RCTs in Medline and Embase.^{25,26} Searches were carried out to identify RCTs concerned with (1) neonates OR prematurity OR

BPD, (2) surfactant OR ventilatory support, and (3) randomized controlled trials. These 3 concepts were linked by the “AND” operator. A variety of search terms was used within each concept. Both free-text and subject-headings (Excerpta Medica Tree terms for Embase, MeSH terms for Medline and CENTRAL) were used. To reduce the number of duplicates, the Embase search was restricted to trials not indexed in Medline. Medline was available via PubMed, Embase via OvidSP, and CENTRAL via DIMDI (Deutsches Institut für medizinische Dokumentation und Information). The format of the searches was adapted as necessary and can be viewed online as Supplemental Information. Results were reported in line with the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) group statement.²⁷

Assessment of Methodological Quality

The assessment of methodological quality complied with Cochrane criteria²⁵: risk of selection bias (quality of randomization, allocation concealment), performance bias (blinding of intervention), detection bias (blinding of outcome assessment), attrition bias (completeness of follow-up), selective reporting (reporting bias), and other features of the study implying a potential for bias were assessed and categorized as low risk, high risk, or unclear risk. Plans existed to contact the study authors and ask for additional information about their trials if necessary.

Data Collection and Analysis

The authors of the present meta-analysis worked independently of each other on selecting the studies, assessing the methodological quality, and extracting the data. At each stage, the authors discussed and resolved any differences that arose. RevMan version 5.1.6 was used for data analysis. The effect that

strategies for avoiding ventilation had on primary and secondary outcomes was calculated by using a random effects model. Odds ratios and 95% confidence intervals (CIs) were reported for all included studies and for the pooled data. A level of statistical significance of $P < .05$ was accepted. For the primary outcome, a number needed to treat (NNT) was calculated. Heterogeneity was estimated by using the χ^2 test and the I^2 value. To assess for publication bias, the treatment effects that avoiding ventilation had on BPD were plotted against SE (log[odds ratio]) in a funnel plot.^{25,28}

RESULTS

The authors identified 3692 records through database searches, and 24 records through other sources (Fig 1). Because of the high number of records retrieved and the different servers used to access the different databases, removing duplicates at this stage was not practicable. A total of 3716 records were therefore screened for eligibility. Of those, 3702 were excluded because they were off-topic or did not meet the inclusion criteria. The remaining 14 records were obtained as full-text articles and assessed for eligibility. Of

these articles, 11 were in English and 3 in Chinese.

Excluded Studies

After full assessment, 7 studies were excluded. One of those was not an RCT.²⁹ Another, the trial of Chu et al,³⁰ compared prophylactic intubation and surfactant application with rescue surfactant in 100 premature infants of <32 weeks' GA, but did not report on BPD or IVH as outcomes. The remaining 5 studies were excluded because they focused on premature infants >30 weeks' GA with mild to moderate RDS.^{31–35}

Included Studies

The characteristics of the 7 RCTs included in the meta-analysis are shown in Table 1. The authors of 6 studies were contacted, and additional information about 4 trials was obtained.^{15,19,36,37} We very much appreciate the cooperation of 2 authors who provided us with previously unpublished, stratified data from their studies.^{19,37} The included RCTs differed from each other with regard to patient maturity, inclusion criteria, and prescribed treatment (Table 1). Although the early trials compared nCPAP with INSURE and/or

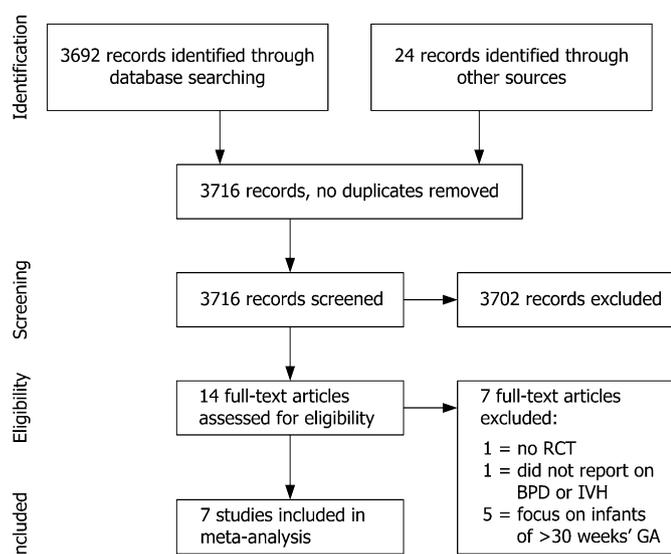


FIGURE 1

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.²⁷

TABLE 1 Characteristics of Included Studies

Author	Study Name	Year	Intervention	Any eMV Except INSURE, %	GA	Randomization	<i>n</i>	Recruitment
Morley et al ¹³	COIN	2008	nCPAP versus mechanical ventilation	59 vs 100	25 ⁰ / ₇ –28 ⁶ / ₇	At 5 min of age	610	1999–2006
Rojas et al ³⁷ ^a	CNRN	2009	nCPAP versus INSURE	43 vs 39	27 ⁰ / ₇ –29 ⁶ / ₇	15–60 min of age	146 ^b	2004–2006
Finer et al ¹⁴	SUPPORT	2010	nCPAP versus mechanical ventilation	83 vs 100	24 ⁰ / ₇ –27 ⁶ / ₇	<1 h of age	1316	2005–2009
Sandri et al ¹⁶	CURPAP ^d	2010	nCPAP versus INSURE	31 vs 33 ^c	25 ⁰ / ₇ –28 ⁶ / ₇	<30 min of age	208	2007–2008
Dunn et al ¹⁵	DRM	2011	3 groups: nCPAP versus INSURE versus mechanical ventilation	52 vs 59 vs 96	26 ⁰ / ₇ –29 ⁶ / ₇	Before delivery	648	2003–2009
Göpel et al ³⁶	AMV	2011	nCPAP ± surfactant during spontaneous breathing versus nCPAP ± mechanical ventilation	33 vs 73	26 ⁰ / ₇ –28 ⁶ / ₇	<12 h of age	220	2007–2009
Kanmaz et al ¹⁹ ^a	Take Care	2013	nCPAP ± surfactant during spontaneous breathing versus nCPAP ± INSURE	42 vs 52 ^a	≤29 ⁶ / ₇	<2 h of age	141 ^b	2010–2011

^a Previously unpublished, stratified data for infants <30⁰/₇ weeks' GA.

^b Number of infants <30⁰/₇ weeks' GA only.

^c Need for any eMV except INSURE in the first 5 d of live.

^d Combining prophylactic surfactant and early nasal continuous positive airway pressure study.

longer-term mechanical ventilation,^{13–16,37} the more recent studies investigated surfactant application during nCPAP via a thin catheter as an alternative to endotracheal intubation and surfactant.^{19,36}

Risk of Bias in the Included Studies

Selection Bias: Random sequence generation was found to be adequate in most trials (low risk), but 2 of the studies did not describe it in detail (unclear risk).^{14,16} Allocation concealment was adequate in all RCTs (low risk). Performance bias and detection bias: All studies were nonblinded, implying a high risk of bias. One RCT used only the physiologic definition of BPD, without blinding the outcome assessment.³⁶ Attrition bias: In the Colombian Neonatal Research Network (CNRN) study, 1 patient was lost to follow-up and excluded from the analysis (low risk).³⁷ In the Delivery Room Management (DRM) study, 3% of the study patients did not receive a cranial ultrasound (low risk).¹⁵ The outcome data of all other studies were complete (low risk). Reporting bias: Six study protocols were registered at independent trial registries before or during the recruitment period (low risk), and the CNRN study was registered only after recruitment was complete (unclear risk). Other sources of bias: Several study protocols gave

cause for concern regarding sampling bias. The DRM study was stopped prematurely after an interim analysis revealed that no statistically significant differences in major outcomes were in sight (low risk).¹⁵ There was unclear risk for sampling bias in the Continuous Positive Airway Pressure or Intubation at Birth (COIN), CNRN, and Take Care trials because clinical judgment of the patient's respiratory status was part of the study entry criteria.^{13,19,37} Additional issues were identified in the Avoiding Mechanical Ventilation (AMV) trial (parental consent and patient recruitment up to 12 hours of age, unclear risk)³⁶ and the CNRN trial (neonates not recruited if expected to be transferred to another hospital because of the parents' health insurance, unclear risk).³⁷ No other potential sources of bias were detected. The funnel plot of all studies with regard to BPD reveals a symmetrical distribution of effect sizes around the mean, indicating a low risk of publication bias. This funnel plot, as well as a detailed characterization of all included studies and of the assessment of methodological quality, is available as supplementary material.

Effects of Intervention

The meta-analysis revealed that applying diverse strategies for avoiding eMV resulted in a statistically significant

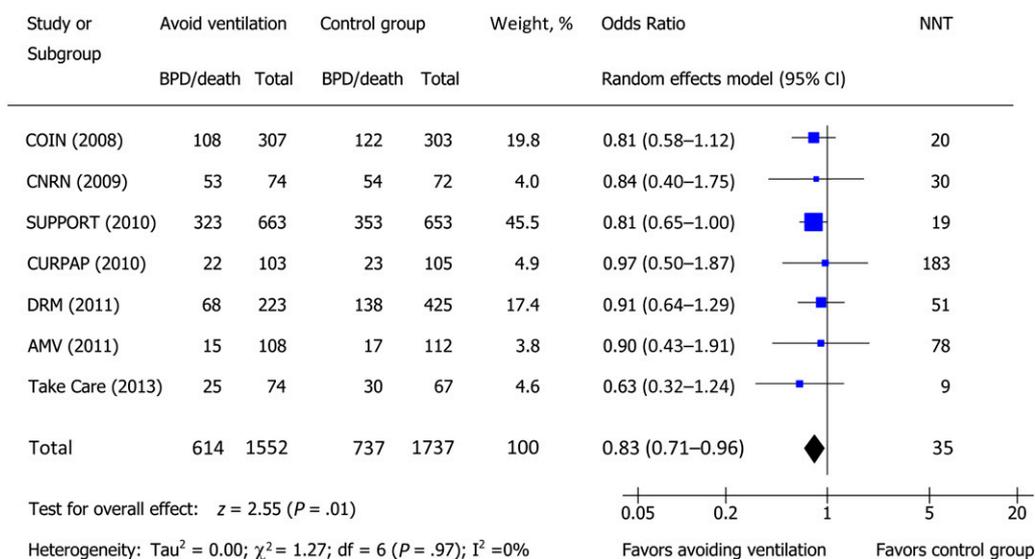
reduction of death or BPD ($P = .01$; Fig 2). The odds ratio (95% CI) was 0.83 (0.71–0.96) with an NNT of 35. Avoiding eMV had no influence on the incidence of severe IVH ($P = .35$; Fig 3). Measures of heterogeneity did not indicate a heterogeneity problem ($\chi^2 < df$ and $P > .60$ in both analyses, as shown in Figs 2 and 3).

DISCUSSION

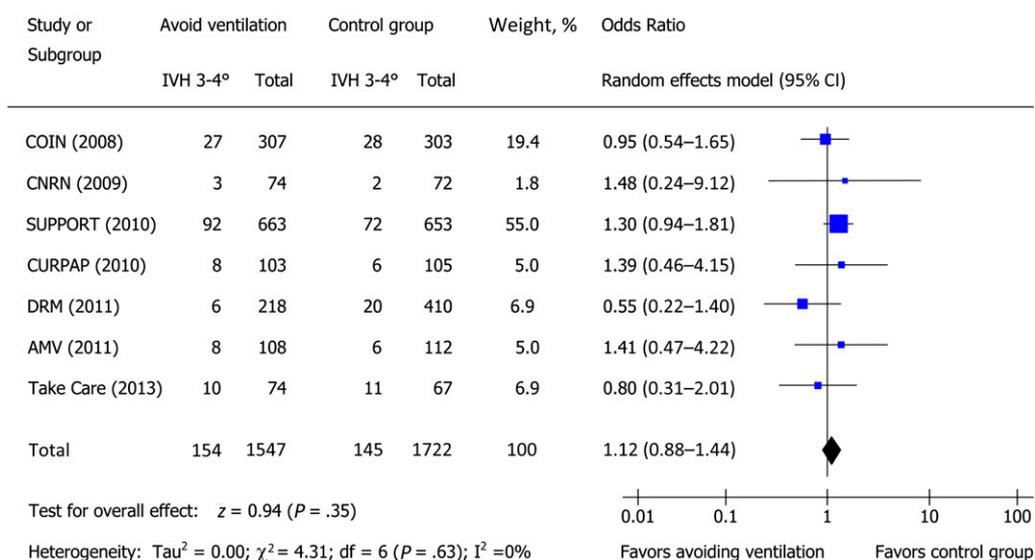
The present meta-analysis of 7 RCTs comprising 3289 patients revealed that avoiding eMV reduced the combined outcome of death or BPD in preterm infants <30 weeks' GA. The risk of developing severe IVH was unchanged.

Quality of Evidence

Assessment of the included RCTs indicated that all studies were of good methodological quality with mostly low risk for bias. The only major issue was the lack of blinding. Although it is virtually impossible to blind clinicians to the intervention, it might be possible to reduce detection bias in the future by using the physiologic definition of BPD,^{23,38} which involves a standardized, time-limited room air challenge with oxygen saturation monitoring for all infants receiving a fraction of inspired oxygen (FiO_2) ≤30% at 36 weeks' postmenstrual age. Still, even with this

**FIGURE 2**

Effect of avoiding eMV on death or BPD.

**FIGURE 3**

Effect of avoiding eMV on IVH.

definition, complete blinding of outcome assessment would be challenging. Furthermore, several studies have revealed that the physiologic definition diagnoses fewer infants with BPD.^{7,14,38} Advocates of the severity-based consensus definition point out that this definition correlates with long-term clinical outcomes³⁹ and that the more rigorous physiologic definition of BPD may miss infants with moderate respiratory impairment that still warrant

closer follow-up.⁴⁰ In summary, a considerable risk of performance and detection bias is present in all included studies, with a special set of problems surrounding the use of supplemental oxygen as a diagnostic criteria for BPD. The risk of sampling bias in studies using clinical criteria for postnatal patient recruitment is considered a minor point. In connection with the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), however, it was

found that protocols prescribing antenatal parental consent also bias the study population (in this case by skewing it toward newborns who were receiving antenatal steroids and whose parents could be approached without language barriers).⁴¹ Although it is possible that some study populations differed from those intended, this was unlikely to reduce the external validity of the meta-analysis because the protocol explicitly allowed inclusion of a broad spectrum

of patients $<30 \frac{0}{7}$ weeks' GA with different degrees of immaturity and severity of lung disease.

Effect on BPD

In spite of substantial differences between study protocols, the meta-analysis results for the primary outcome death or BPD were remarkably homogenous. Regardless of the population studied and the strategy used, avoiding eMV consistently led to a reduction in the incidence of death or BPD in all trials, with odds ratios ranging from 0.63 to 0.97 (Fig 2) and a statistically significant effect in the meta-analysis (odds ratio, 0.83 [95% CI, 0.71–0.96]). This matches large observational studies, which revealed that an increase in the primary use of nCPAP over time was associated with a lower BPD risk in infants <29 weeks' GA⁷ and in extremely low birth weight infants.⁵ A recently updated Cochrane review conducted a subgroup analysis that compared prophylactic surfactant administration with selective surfactant treatment of established RDS in preterm infants <30 weeks' GA.⁴² The Cochrane authors identified 2 studies that prescribed routine application of nCPAP in the control group (SUPPORT and the DRM trial). In conformity with our results, their meta-analysis revealed an increase in death or BPD when endotracheal intubation and surfactant were applied prophylactically (risk ratio, 1.12 [95% CI, 1.02–1.24]).

So although there is a consensus that infants who require early eMV for severe RDS should be given surfactant in a timely fashion,⁴³ available data indicate that stabilizing premature infants <30 weeks' GA on nCPAP alone, thereby avoiding eMV altogether, is a viable and effective way of reducing BPD. This observation is in line with the current understanding of the pathogenesis of BPD. A considerable number of studies in animal and human neonates have

revealed that a pulmonary inflammatory response is a crucial factor in BPD development.²¹ Pulmonary inflammation might be of antenatal origin⁴⁴ but might also be provoked by eMV,^{20,45} supplemental oxygen,⁴⁶ or postnatal infections.⁴⁴ In an extremely preterm lung, eMV triggers an inflammatory cascade, which involves chemokines and other proinflammatory cytokines, transmigration of inflammatory cells to airspaces, secondary lung injury by proteases, and dysregulation of growth factors, leading to fibrosis and abnormal lung development.^{12,21,45} Animal studies reveal that only 2 hours of postnatal pressure-limited ventilation induced an inflammatory response in the alveolar wash fluid of premature lambs,⁴⁵ and lambs receiving 2 hours of continuous positive airway pressure were found to have lower indicators of acute lung injury and better lung compliance than lambs that were mechanically ventilated.²⁰ This supports the hypothesis that avoiding the inflammatory response secondary to eMV may reduce BPD. As preterm lungs appear to be particularly vulnerable during the first few hours of life,^{47,48} early intubation should be avoided. Special caution should be exercised during newborn resuscitation, as seemingly gentle mask ventilation may also overexpand the lungs.⁴⁹

Other mechanisms may contribute, albeit to a lower extent, to BPD reduction in infants who are never intubated. Firstly, noninvasive respiratory support may prevent direct complications of a difficult intubation, such as vocal cord dysfunction or subglottic stenosis, which may lead to prolonged ventilation and ventilator-induced lung injury.^{50,51} Secondly, the absence of an endotracheal tube may avoid reflex-induced apnea occurring in response to mechanical stimulation of the laryngeal mucosa.⁵² Thirdly, noninvasive respiratory support preserves normal laryngeal

function, allows normal mucociliary clearance of lung secretions, and may prevent secondary lung damage by reducing the incidence of ventilator-associated pneumonia.^{44,53}

Effect on IVH

Avoiding eMV in very premature infants means that a considerable number of them will later need rescue intubation because of hypercapnic respiratory failure. On the one hand, there are substantiated concerns about the association between hypercapnia and IVH in preterm infants,⁵⁴ especially during the first days of life.⁵⁵ Moreover, hypercapnia can go unnoticed if respiratory drive is poor, and transcutaneous CO₂ monitoring is not popular because the electrodes can cause heat damage on extremely immature skin.⁵⁶ On the other hand, mild hypercapnia has long been regarded as safe in premature infants <1000 g, and permissive hypercapnia can be used as a way of reducing eMV and improving pulmonary outcomes.⁵⁷ The results of the present meta-analysis revealed no difference in the incidence of severe IVH between the intervention group and the control group, which indicates that the strategies applied to avoid eMV in the included RCTs were generally safe (Fig 3). The measures of heterogeneity suggest that different odds ratios for IVH in individual studies may be explained by chance alone, and there was no apparent relationship between prescribed Pco₂-thresholds for intubation and higher incidences of IVH.

Clinical Implications

Although avoidance of eMV reduced the combined outcome of death or BPD in the meta-analysis, deciding to manage a very premature infant solely with noninvasive respiratory support is often extremely difficult because we lack evidence-based thresholds for intubation and surfactant treatment. In the meta-analysis, the effect on BPD of

avoiding eMV was consistent across all studies included in spite of the different strategies they applied to avoid eMV. From a safety point of view, early nCPAP carries an increased risk of pneumothorax if thresholds to administer surfactant are set high (9% in the COIN and CNRN trials), whereas pneumothorax rates decrease to 2% to 3% if surfactant is given during the first hour of life.^{13,37} In this regard, nCPAP with surfactant treatment during spontaneous breathing is a promising option because it allows to combine avoidance of eMV with early surfactant administration.^{17–19,36} It is worth noting that 33% to 83% of study patients in the noninvasive treatment groups needed eMV at some point during their clinical course (Table 1). It is possible that these patients still benefited with regard to BPD reduction because eMV was avoided during the postnatal transition period when their lungs were particularly vulnerable.^{20,47,48} That said, only a subset of moderately ill patients will benefit from the doctor's intention to withhold intubation, because stable newborns will be managed with noninvasive respiratory support anyway, whereas critically ill patients will still require immediate intubation. In the present meta-analysis, this is reflected by the moderate influence on the primary outcome of death or BPD and by the high NNT of 35.

Consequently, a modern approach to BPD prevention in premature infants <30 weeks' GA does not overestimate the value of avoiding eMV, but applies a sophisticated, individualized clinical strategy. This may include established measures such as low oxygen resuscitation⁴⁶ and early use of caffeine.⁵⁸ It could also involve interventions that have been investigated more recently, such as macrolide treatment of preterm infants colonized with ureaplasma,⁵⁹ and volume-targeted ventilation.⁶⁰

Implications for Research

Although 5 of the 7 RCTs in the meta-analysis investigated nCPAP without surfactant as a way of avoiding eMV in infants of <30 weeks' GA, more data are needed about other noninvasive treatment methods and their effect on BPD.

Nasal intermittent positive pressure ventilation (nIPPV) has been shown to increase the beneficial effects of nCPAP in the treatment of apnea of prematurity^{61,62} and in the prevention of neonatal extubation failure.⁶³ Several single-center RCTs indicate that nIPPV may also be a viable alternative to nCPAP as an initial treatment of RDS.^{62,64–66} Recent meta-analyses have revealed that, compared with nCPAP, nIPPV reduced the need for eMV within the first 72 hours of life⁶⁷ and reduced the combined outcome of death or BPD.⁶⁸ However, the individual study results varied considerably. Synchronized nIPPV was not associated with further benefits when compared with conventional nIPPV in a retrospective study.⁶⁹ More recently, 2 crossover studies have revealed that neurally adjusted ventilatory assist, where the ventilator is triggered by the electrical activity of the diaphragm, improves synchronization and gas exchange in preterm infants.^{70,71} Future RCTs need to reveal whether this new technology also improves long-term outcomes. Nasal high frequency oscillatory ventilation (nHFOV) is another promising form of noninvasive respiratory support, which avoids the problem of breath synchronization. Bench testing revealed that CO₂-elimination was more effective during nHFOV than during nIPPV.⁷² A small interventional study in 14 very low birth weight infants on nCPAP revealed similar benefits when Pco₂ was measured before and after 2 hours of nHFOV.⁷³ Other observational studies revealed successful use of nHFOV as rescue therapy for nCPAP failure⁷⁴ and in the

postextubation period.⁷⁵ To explore the future role that nHFOV could play in the treatment of RDS, further research on effectiveness and safety is needed.

If rescue surfactant is administered without endotracheal intubation for more severe RDS, its benefits could possibly be combined with those of noninvasive respiratory support. Surfactant can be administered via a thin endotracheal catheter placed intratracheally by using a laryngoscope and a Magill forceps during spontaneous breathing and ongoing nCPAP treatment.¹⁷ Alternatively, a semirigid vascular catheter can be guided through the vocal cords without a trochar or forceps.¹⁸ Laryngeal mask airways have been used for surfactant administration in a study of premature infants between 880 and 2520 g,⁷⁶ and a recent RCT has confirmed that this technique achieves effective surfactant delivery.⁷⁷ Aerosolized surfactant would be the least invasive and probably most desirable way of administering surfactant. Progress has recently been made toward solving the technical problems of surfactant nebulization by using vibrating membrane nebulizers,^{78–80} but more clinical data are needed on the efficacy of aerosolized surfactant and of other innovative methods of administering surfactant. Moreover, future RCTs should investigate the optimal timing of surfactant administration. With respect to the study design, the mode of respiratory support should be similar when surfactant timing is studied, and vice versa.

RCTs have also revealed that sustained inflations⁸¹ and heliox⁸² reduce the risk of infants having to undergo eMV, and late recurrent dosing of surfactant has shown some promise for shortening the duration of eMV in intubated infants.⁸³ These interventions need to be investigated as complementary strategies for reducing BPD.

Limitations of the Meta-analysis

There are several limitations to this meta-analysis. Firstly, the exclusion of abstracts and conference proceedings implies a risk of publication bias. However, the funnel plot does not indicate any such bias, and our method ensured that the included RCTs had undergone a rigorous peer review. Secondly, as the RCTs differed with regard to inclusion criteria, treatment protocol, and number of patients recruited in each study, this might have impacted the effect size of BPD reduction in the meta-analysis. The differences included the study patients' GA, the strategy used to avoid eMV, and timing and dosage of methylxanthine and surfactant treatment. Thirdly, due to constraints of time and resources, the meta-analysis was designed to only investigate severe IVH as a secondary

outcome. A more detailed meta-analysis needs to investigate the impact that avoiding intubation has on other adverse outcomes of prematurity and on clinical complications such as pneumothorax.^{13,37} Because eMV has been associated with reduced cerebral blood flow and cerebral palsy in very premature infants,^{84,85} future meta-analyses should include neurodevelopmental outcomes.

CONCLUSIONS

The present meta-analysis indicates that avoiding eMV reduces the incidence of death or BPD in premature infants <30 weeks' GA without increasing the risk of IVH. However, with an NNT of 35, the beneficial effect was small. Avoiding intubation and subsequent ventilation through an endotracheal tube may only be one

component of a comprehensive strategy to reduce BPD in this population. Future studies need to explore the role of nIPPV and nHFOV in the primary treatment of neonates in the delivery room and to investigate alternative methods of administering surfactant.

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