Prevention of ventilator induced lung injury in preterm infants with respiratory distress syndrome: PreVILIG
Cools, F.A.A.M.

Citation for published version (APA):
SUMMARY

1. Introduction

Despite the advances in neonatal care, still a considerable proportion of prematurely born infants develop chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD). Mechanical ventilation is a well recognized cause of ventilator induced lung injury (VILI) and hence, of BPD.

Several new interventions and new techniques have been tested in preterm infants requiring mechanical ventilation in order to reduce ventilator induced lung injury and hence, the incidence of this chronic condition. High-frequency ventilation (HFV) is such a new, promising technique which proved to cause less lung damage than conventional ventilation (CV) in animal experiments. Another potentially beneficial intervention is paralyzing the infant during mechanical ventilation using neuromuscular blocking agents, because it eliminates asynchronous spontaneous breathing efforts of the baby and thus facilitates mechanical ventilation of the newborn.

In this thesis we aimed to investigate the effectiveness of two interventions, namely the elective use of HFOV versus CV in preterm infants with respiratory failure and the routine use of neuromuscular paralysis in ventilated newborn infants, in reducing the risk of bronchopulmonary dysplasia, using the available evidence from randomized controlled trials.

2. Aggregate data meta-analysis of randomized trials comparing elective HFOV with CV in preterm infants with respiratory failure

Chapter 2 describes the systematic reviews with aggregate data meta-analysis we performed of the randomized controlled trials comparing the elective use of HFV with CV in preterm infants. The first meta-analysis was performed in 1999 and looked at high-frequency ventilation in a broad sense, including 10 trials and a total number of 1345 infants. The systematic review which we performed in collaboration with the Cochrane Neonatal Review Group focused on high-frequency oscillatory ventilation (HFOV), and was updated most recently in April 2009.

Seventeen eligible trials with a total number of 3652 study infants were included. Meta-analysis comparing HFOV with CV revealed no evidence of effect on mortality at 28 - 30 days of age or at approximately term equivalent age. These results were consistent across studies and in subgroup analyses. The effect of HFOV on BPD in survivors at term equivalent gestational age was inconsistent across studies and the reduction was of borderline significance overall. The effect was similar in trials with a high lung volume strategy for HFOV targeting at very low fractional inspired oxygen concentration (FiO₂) and trials with a high lung volume strategy with somewhat higher or unspecified target FiO₂. Subgroups of trials showed a significant reduction in BPD with HFOV when no surfactant was used, when piston oscillators were used for HFOV, when lung protective strategies for CV were not used, when randomisation occurred at two to six hours of age, and when an inspiratory-to-expiratory-ratio of 1:2 was used for HFOV. In the meta-analysis of all trials, pulmonary air leaks occurred more frequently in the HFOV group.

In some studies, short-term neurological morbidity with HFOV was found, but this effect was not statistically significant overall. The subgroup of two trials not using a high volume strategy with HFOV found increased rates of grade 3 or 4 intraventricular haemorrhage and of periventricular leukomalacia. An adverse effect of HFOV on long-term neurodevelopment was found in one large trial but not in the five other trials that reported this outcome. The rate of retinopathy of prematurity is reduced overall in the HFOV group.
Our conclusion was: 1) that there is no clear evidence that elective HFOV offers important advantages over CV when used as the initial ventilation strategy to treat preterm infants with acute pulmonary dysfunction; and 2) that, although there may be a small reduction in the rate of BPD with HFOV use, the evidence is weakened by the inconsistency of this effect across trials and the overall borderline significance. However, this systematic review has limitations because it is unable to explain the heterogeneity which exists between trial results. Thus, although our systematic review provides a comprehensive overview of the available evidence from randomized controlled trials regarding the possible benefits and harms of HFOV in preterm infants, it is not able to guide neonatologists in their daily practice.

3. Trial-level and patient-level factors modify the observed treatment effect of HFOV on BPD: current meta-analyses revisited.

Interpretation of meta-analyses of randomized controlled trials comparing HFOV with CV has been difficult because of unexplained heterogeneity between trial results. Both trial-level factors, such as the ventilation strategy or the ventilator device, as well as patient-level factors, i.e. patient characteristics, have been considered as possible effect modifying factors. Conventional meta-analyses have used different techniques to explore the importance of those factors in modifying the observed treatment effect.

In Chapter 3 we give an overview of the analyses which have been performed in the currently available meta-analyses to explore possible effect modifiers, and we highlight the limitations of the methodologies used.

Four meta-analyses summarizing 14 to 17 randomized trials were identified. With regard to trial-level factors, the ventilator device, the ventilation strategy and the timing of initiation of HFV have been explored as possible treatment effect modifiers. Meta-analytic techniques used were subgroup analyses, cumulative meta-analysis and meta-regression analysis. Subgroup analyses were not entirely consistent across meta-analyses because of differences in subgroup definition and inconsistencies in trial classification. In addition, they were limited because of the inability to include certain trials because of the specific trial design. Interpretation of results from subgroup analyses was hampered by unexplained persistent treatment effect heterogeneity. A main limitation of meta-regression analysis was the small number of included trials. This resulted in low statistical power and hence, in imprecise effect estimates with very wide confidence intervals.

With regard to patient-level factors, only gestational age at birth and birth weight have been explored as possible effect modifiers, and meta-regression analysis was the only meta-analytic technique used. Besides the abovementioned limitation of meta-regression analyses, another important disadvantage of using this technique to explore relations between patient characteristics and observed treatment effect is the fact that, because they are based on summary data from the trial reports, they explore the relation with averages of patients' characteristics for the whole study population instead of true individual patient characteristics. Both false positive associations (because of confounding) as well as false negative associations (because of limited range of variation of averages between trials) can occur. Therefore, applicability of the results to the individual patient is problematic.

In conclusion, the currently available meta-analyses of randomized trials are not able to provide conclusive answers to the important clinical questions regarding the use of HFOV in preterm infants. Although the roles of the type of ventilator and the ventilation strategy have been investigated, the available analyses have important limitations and conclusions can only be drawn with vast caution. Little is known about the role of patient characteristics as potential effect modifiers for HFV. Identified limitations of the existing meta-analyses are
mainly caused by the fact that they are based on ‘aggregate data’, meaning that data on determinants and outcomes were extracted from trial reports. Information in trial reports is often incomplete or imprecise. More importantly, aggregate data are not efficient when exploring treatment effect modification by patient-level factors.

4. PreVILIG, an international Collaborative Group, and the prospective development of a protocol for an individual patient data meta-analysis.

To counter the challenges unmet by the existing meta-analyses a Collaborative Group was formed in 2006 with the investigators of the original randomized controlled trials. The group was called the Prevention of Ventilator Induced Lung Injury collaborative Group or PreVILIG Collaboration. Through a number of Collaborative Group Meetings a protocol was prospectively developed to perform a systematic review and meta-analysis based on individual patient data (IPD). This means that for trials where the original raw patient data were still available, pre-specified data items regarding baseline characteristics, study interventions and neonatal outcomes would be collected for each individual infant randomized in those trials.

In Chapter 4 we present the protocol in full detail. It describes every step of the project. Agreement was reached with all the collaborators regarding the data items to be collected for each randomized infant and the outcome definitions to be used. The data items concerned patient baseline characteristics, experimental (HFOV) and control (CV) intervention, co-interventions, blood gas values and neonatal outcomes. A detailed analysis plan was developed prospectively. Individual patient data had to be anonymized before being sent and would be stored and managed centrally by a Data Management Team. Original investigators would remain the custodian of their trial data at all times and would be involved in every step of the project. Results of the meta-analyses would be presented to and discussed with all the Collaborators in a Collaborative Group Meeting, after which results would be published on behalf of the PreVILIG Collaboration.

An IPD meta-analysis has several advantages over an aggregate data meta-analysis. The quality of the data will improve because it allows defining patient characteristics and outcomes uniformly across trials. For certain trials it might be possible to obtain information on previously unreported outcomes. Information will become available on the actually applied ventilation strategies in the trials. Most importantly, it will allow investigating the effect of HFOV in certain subgroups of infants based on their risk profile.

5. Elective HFOV versus CV in preterm infants with respiratory failure: results from a meta-analysis based on individual patient data.

Chapter 5 described the main results of the individual patient data meta-analysis. Eighteen trials were eligible for inclusion. We were unable to retrieve additional information or trace the original investigators from one unpublished trial. The remaining 17 eligible trials included a total of 3652 infants. In 7 trials, the individual patient data (n = 430) were lost or unavailable. Individual patient data were collected from 10 trials including a total of 3229 infants (89% of randomized infants).

For all infants ventilated with HFOV, the relative risk of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age was 0.95 (95% confidence interval 0.88-1.03) and of death or severe adverse neurological event 1.00 (95% CI 0.88-1.13). The type of ventilator or ventilation strategy did not modify the overall effect. No particular subgroups of infants based on gestational age, birth weight for gestation, initial lung disease severity or exposure to antenatal corticosteroids benefited more or less from HFOV. In contrast with infants
randomized within 1 hour or more than 4 hours after intubation, infants randomized between 1 to 4 hours after intubation benefited significantly from HFOV: relative risk of death or bronchopulmonary dysplasia or severe adverse neurological event 0.82 (95% CI 0.72-0.94).

In conclusion, using individual patient data meta-analysis of 89% of the totality of randomized babies entered into trials in this field, HFOV appears similarly effective to conventional ventilation for important neonatal outcomes, namely death, oxygen dependency and neurological injury, alone and in combination. The effect of HFOV is not modified by several patient characteristics. However, the timing of initiation of HFOV appears to modify the effect with a better outcome if HFOV is started moderately early.

Results from subgroup analyses should be interpreted with caution because of the risk of both false positive findings (multiple testing) as well as false negative findings (small number of infants in subgroup). Furthermore, the bi-variate “two-stage” approach we used for the meta-analyses might be insufficient to explore fully the independent relation of each determinant with the outcome. Thus, further exploration using a multi-variate modelling “one-stage” approach is warranted.

6. Variation in ventilation settings and short term ventilation parameters explains heterogeneous results within and among clinical trials of elective HFOV in preterm infants: analysis based on individual patient data.

Mechanical ventilation is a complex intervention, delivered by a machine which is “driven” by physicians with various levels of knowledge, experience and beliefs. Thus, although HFOV and CV may be used as common terms for ventilation modes across trials, ventilation strategies may have been interpreted and developed in various ways. Although most of the recent randomized controlled trials comparing HFOV with CV used similar strategies, i.e. a “high lung volume strategy” for HFOV and a “lung protective strategy” for CV, it has been suggested that important differences exist between trials. So far, the subgroup analysis of the IPD meta-analysis has not fully unravelled the complexity of this.

In Chapter 6 we describe the differences in the mechanical ventilation which was actually applied to the study infants in the randomized trials, with respect to the timing of initiation of HFOV, the ventilation strategies for HFOV and CV, and the treatment with exogenous surfactant, using the original individual patient data from the trials.

Individual patient data on ventilator settings, blood gas values and surfactant therapy were available from 8 trials including a total number of 2309 infants. In all trials except one, the children allocated in the HFOV-group received significantly higher mean airway pressures in the first hours after randomization than those in the CV-group. The percentage of children in the HFOV-group with a fractional inspired oxygen concentration after lung volume recruitment of 0.40 or less varied across trials between 35% and 100%. Initial ventilator rate for children in the CV-group varied across trials between a median of 30 breaths per minute (IQR 21-40) and 60 breaths per minute (IQR 60-70); for peak inspiratory pressure between a median of 17 mmHg (IQR 16-17) and 24 cmH2O (IQR 22-27). Average partial carbon dioxide tension in the first 72h after randomization in the CV-group of these trials varied between a median of 36 mmHg (IQR 30-42) and 52 mmHg (IQR 50-59). Time lapeses between birth and initiation of HFOV and surfactant administration varied widely between trials.

In conclusion, the actually applied ventilation strategies differ substantially between trials, both for HFOV as well as for CV. Specifically, optimal lung volume recruitment, as reflected by a low fractional inspired oxygen concentration in the first hours after initiation of HFOV, was achieved in a highly variable proportion of study infants in the trials. And although recent trials mostly used a higher initial ventilator rate and a lower initial peak inspiratory pressure
for infants in the CV-group, quite some variation existed in the ventilator settings of CV between trials. With regard to the timing of initiation of HFOV and the timing of the first surfactant dose, very different strategies were used in these randomized trials. Given the recent insight in pathophysiological mechanism of BPD development, it is likely that these differences in respiratory management of preterm infants requiring mechanical ventilation explain – at least in part – the variation in observed treatment effects of HFOV on BPD. Differences in baseline characteristics of the study populations may contribute to a lesser extend to the heterogeneous results as well. Further exploration of the independent relationships between all relevant determinants and the risk of BPD is needed.

Differences in baseline characteristics of the study populations may contribute to a lesser extend to the heterogeneous results as well. Further exploration of the independent relationships between all relevant determinants and the risk of BPD is needed.


Neuromuscular paralysis during mechanical ventilation is also an intervention which has the potential to reduce the risk of ventilator induced lung injury because it eliminates asynchrony between the infant and the ventilator. In Chapter 7 we describe the results of a systematic review and meta-analysis of randomized controlled trials comparing the routine use of neuromuscular blocking agents versus no use or the selective use of neuromuscular blocking agents in newborn infants receiving mechanical ventilation.

Six randomized controlled trials, including a total of 486 infants, reported on the effectiveness of neuromuscular paralysis in ventilated newborn infants, and were included in the review. The routine use of neuromuscular blockade with pancuronium in a selected population of ventilated preterm infants breathing in asynchrony with the ventilator results in a reduction of intraventricular haemorrhage (relative risk 0.55, 95% CI 0.34, 0.89; risk difference -0.24, 95% CI -0.41, -0.07) and of pneumothorax (relative risk 0.29, 95% CI 0.11, 0.77; risk difference -0.43, 95% CI -0.64, -0.23). No definite conclusions can be drawn regarding the effect on long term pulmonary and neurological outcome or regarding the safety of prolonged use of pancuronium in ventilated preterm infants. Because of the lack of data from randomized trials and because of limited external validity of the trials, the routine use of pancuronium in ventilated preterm infants cannot be recommended based on current evidence. No data are available from randomized controlled trials about the effects of neuromuscular blocking agents other than pancuronium.

An important limitation of this systematic review is the poor applicability of its results in current clinical practice, since the majority of included trials were carried out in the pre-surfactant and pre-antenatal corticosteroids era.

8. General discussion

In Chapter 8 we reflect on the merits and the limitations of the aggregate data meta-analysis in estimating the benefits and risks of the use of HFOV in preterm infants. Despite the fact they give a comprehensive overview of the available evidence, the aggregate data meta-analyses seem to be unable to unravel the complex interactions between possible effect modifiers and observed treatment effect. Their limitations are mainly related to the fact that they are based on aggregate data.

Next, we reflect on the advantages that our IPD meta-analysis had over the existing aggregate data meta-analyses, such as improved quality of the data, uniform definitions of outcomes and subgroup analyses by patient characteristics.

We highlight the limitations of the IPD meta-analysis, such as the problem of missing data and the weaknesses of the “two-stage” approach.
9. Conclusions and implications

Overall, HFOV and CV are similarly effective in preventing death or BPD or severe brain injury in preterm infants with respiratory failure.

No specific subgroups of preterm infants, based on gestational age at birth, birth weight for gestational age, antenatal treatment with corticosteroids or initial lung disease severity, have been identified who benefit more from HFOV than others.

Although the results need to be interpreted cautiously, the timing of initiation of HFOV seems to be a factor which modifies the effect of HFOV, with a better outcome if HFOV is started moderately early. Further analyses are warranted to determine whether it is the child’s postnatal age per se or the time lapse between intubation and the start of HFOV which modifies the treatment effect of HFOV.

Successful optimization of lung volume with HFOV, as reflected by a low oxygen requirement after alveolar recruitment, was highly variable across trials and generally less effective as could be expected. Obtaining the set targets for lung volume recruitment proves to be a challenge in clinical practice, and must be further improved in order to reduce BPD.

A number of issues need further exploration. The exact role of the timing of initiation of HFOV and of the variation in the actually delivered “high lung volume strategy” with HFOV as well as in the actually delivered “lung protective strategy” with CV needs to be clarified further. This can be done using existing data in a multivariate modelling approach.

New trials regarding the use of HFOV should be focusing on the optimal timing of surfactant treatment during HFOV, or on the role of HFOV in infants with respiratory distress syndrome who fail a trial with non-invasive respiratory support. In those trials, attention should go to the efficiency of the lung volume recruitment strategy of HFOV, and HFOV should be compared with the most recent modes of CV.

A number of limitations were encountered in our IPD meta-analysis because it was retrospective in design. This could be overcome by planning IPD meta-analyses prospectively. In order to achieve this, international collaboration between neonatologists over the world is of great importance.