Prevention of ventilator induced lung injury in preterm infants with respiratory distress syndrome: PreVILIG
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CHAPTER 8

GENERAL DISCUSSION
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8.1 Summarizing the main findings

- Our meta-analysis of randomized controlled trials comparing high-frequency oscillatory ventilation (HFOV) with conventional ventilation (CV) in preterm infants with respiratory failure shows a small, but statistically significant benefit reducing the risk of bronchopulmonary dysplasia.

- These results are, unfortunately, difficult to apply to the care of the individual patient because of significant heterogeneity between trial results.

- Important questions regarding the clinical indications and the practical application of high-frequency oscillatory ventilation in preterm infants persist because the observed treatment effect is probably modified by trial-level and patient-level factors. Currently available trials and meta-analyses are unable to answer these questions. The limited utility of the existing meta-analyses for clinical care are due to the fact that they are based on summary data extracted from the trial reports.

- To address these clinical questions, an international Collaborative Group was formed with the investigators of the original randomized controlled trials: the Prevention of Ventilator Induced Lung Injury collaborative study Group or PreVILIG Collaboration. Its aim was to perform a meta-analysis based on the original individual patient data from the trials.

- This individual patient data meta-analysis shows that, for elective treatment of respiratory distress in preterm infants, the combined outcome of death or bronchopulmonary dysplasia and the risk of neurological harm are similar for high-frequency oscillatory ventilation and conventional ventilation. The effect of high-frequency oscillatory ventilation is not modified by several patient-related characteristics such as gestational age at birth, being small-for-gestational-age, antenatal treatment with corticosteroids or initial lung disease severity. However, the timing of initiation of high-frequency oscillatory ventilation appears to modify the effect with a better outcome if high-frequency oscillatory ventilation is started early. The effect of high-frequency oscillatory ventilation is not modified by the ventilator type or the ventilation strategy.

- Our analysis of individual patient data also shows that differences exist between randomized trials regarding important aspects of ventilatory management, such as the timing of initiation of high-frequency oscillatory ventilation, the ventilation strategy of both high-frequency oscillatory ventilation and conventional ventilation, and the treatment with exogenous surfactant. It is very likely that these differences contribute to the heterogeneity in observed treatment effect with regard to the occurrence of bronchopulmonary dysplasia between trials.

- Although there may be some benefit in terms of reduced risk of severe intracranial haemorrhage in infants breathing in asynchrony with the ventilator, there is no evidence that routine neuromuscular paralysis in preterm infants receiving mechanical ventilation reduces the risk of bronchopulmonary dysplasia. However, applicability of these results in current clinical practice is limited because included trials were mainly done in the pre-surfactant and pre-antenatal steroids era.
8.2 Aggregate data meta-analyses of randomized controlled trials comparing HFOV with CV in preterm infants with respiratory distress: merits and limitations.

The controversy about the efficacy and safety of the elective use of high-frequency ventilation in preterm infants with respiratory failure has been going on ever since the disappointing and worrisome results of the first large randomized controlled trial, the HIFI trial, were spread over the world.\(^1\) After the HIFI trial was heavily criticized for not using an appropriate “open lung” strategy with HFOV,\(^2\) everyone expected that subsequent trials which applied the correct high lung volume strategy with HFOV would reproduce the lung protective effects from HFOV as seen in animal experiments.\(^3\)\(^-\)\(^5\) Confusion among neonatologists and pulmonologists only increased when the results of those trials proved to be inconsistent, with some trials showing benefit,\(^6\) other trials showing no effect,\(^7\) and some trials even showing harm.\(^8\)

A systematic review with meta-analysis is very helpful in a situation like this because it rates the methodological quality of the various different studies, it increases the precision of the effect estimate by statistically combining the results of the individual trials, and it offers the opportunity to explore the reasons for heterogeneity between results of individual trials.\(^9\)

The first two meta-analyses on this topic were published in 1997 by an Australian group under the aegis of the Cochrane Collaboration,\(^10\) focusing on high-frequency oscillatory ventilation and including four randomized controlled trials (total number of 946 infants), and in 1999 by our group,\(^11\) looking at high-frequency ventilation in a broader sense and including 10 trials (total number of 1345 infants). Later, these 2 groups joined forces and updated the Cochrane review regularly.\(^12\) Also, other meta-analyses have been published since then.\(^13\)\(^,\)\(^14\)

Our conclusion in the most recent update of the Cochrane review\(^15\) 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 occurrence of bronchopulmonary dysplasia (BPD) with HFOV use, the evidence is weakened by the inconsistency of this effect across trials and the overall borderline significance.

In the Cochrane review,\(^15\) we have used subgroup analysis as the method to explore the heterogeneity in observed treatment effect between trials. Although commonly used in meta-analyses, this methodology has a number of pitfalls.

First, subgroup analyses which are designed post hoc, i.e. once the results of the meta-analyses are known, should be regarded as exploratory or hypothesis generating, because their design can be motivated by inspection of the results.\(^16\) Results of post hoc subgroup analyses should therefore always be interpreted with caution. Although several of the subgroup analyses in our reviews were defined a priori in the first, original review protocol (surfactant, HFOV strategy), other subgroup analyses have been added in subsequent updates of the review as our knowledge regarding the importance of the ventilator device (i.e. oscillator versus flow interrupter), ventilator settings (the inspiratory-to-expiratory-time ratio) or the ventilation strategy of conventional ventilation (i.e. lung protective or not) improved. However, the subgroup analyses in our reviews all have a clear pathophysiological rationale and are supported by evidence from experimental or clinical studies.

Second, in order to interpret results from subgroup analyses correctly, it has recently been recommended to perform a test for interaction to assess whether there is a statistically significant difference in treatment effect between the subgroups\(^17\) rather than interpreting the treatment effects within the subgroups individually. Currently, Review Manager Software® does not allow testing for interaction between subgroups easily. We therefore used another accepted method in our review to assess differences in treatment effect between subgroups,
namely by looking at the overlap of the confidence intervals of the effect estimates of the different subgroups.\textsuperscript{18}

Third, subgroup analyses often increase the total number of analyses such that it becomes very likely to find a statistically significant result simply by chance.\textsuperscript{19} This potential flaw has been limited in our review by pre-specifying subgroup analyses, ensuring that they are based on a clear rationale, and by limiting the subgroup analyses to the clinically most relevant outcomes. Nevertheless, we recognize that the risk of finding spurious results still exists. Therefore, ‘significant’ treatment effects within subgroups should be interpreted with caution.

Specific to the topic of this systematic review of trials comparing HFOV to CV, additional problems exist with the subgroup analyses.

The subgroup analysis by HFOV strategy, where trials are categorized into 2 subgroups (i.e. high lung volume strategy or not), probably oversimplifies the actual variation in ventilation strategies that exists between trials. There are indications from the trial reports that the “high lung volume” strategies for HFOV actually show important difference among trials\textsuperscript{20} and that they may therefore not be comparable. Furthermore, the subgroup analysis by CV strategy is limited by the fact that the information which is required to classify trials into the correct subgroup is often incomplete, lacks sufficient detail (e.g. very wide target ranges for conventional ventilator settings), or is simply not reported at all.

A final limitation of the Cochrane review is related to the fact that the studies have been carried out over a long period of time during which obstetric and neonatal practices have changed importantly. The risk profile of the preterm infant has changed radically with the increasing use of antenatal corticosteroids\textsuperscript{21} and with improving technologies for neonatal intensive care. In addition, new therapies with great impact on neonatal outcome, such as the administration of exogenous surfactant and the postnatal treatment with corticosteroids,\textsuperscript{22,23} have emerged. Our systematic review does not take the impact into account that these changes might have had on the observed treatment effect of HFOV in the trials, beyond the subgroups analyses described (i.e. trials that used surfactant in all babies vs. those who did not).

Other published meta-analyses have used other methodologies to explore the heterogeneity in observed treatment effects between trials, such as cumulative meta-analysis\textsuperscript{13,14} and meta-regression analysis.\textsuperscript{24} Cumulative meta-analysis clearly shows the impact of new studies on prior pooled results. However, it must be stressed that any apparent association between a change in observed treatment effect and a trial-level factor, such as the ventilation strategy of CV in this case, is purely observational and therefore, subject to confounding by co-variables.\textsuperscript{25} The same remark holds for meta-regression analysis.\textsuperscript{26} In addition, meta-regression analysis has been found to be of little value in detecting associations between heterogeneous treatment effects and patient-level factors.\textsuperscript{27}

The limitations of the currently available systematic reviews are mainly related to the fact that they are based on information extracted from the trial reports. Besides the fact that this information is often incomplete or reported in various ways, the main disadvantage is the fact that only summary data of study populations are available for the analyses. The existing aggregate data meta-analyses are particularly limited in their ability to detect relations between the preterm infant’s individual risk profile and the treatment effect of HFOV and, therefore, cannot help targeting the use of HFOV at preterm infants most likely to benefit.

In conclusion, although currently available systematic reviews with aggregate data meta-analysis provide an up-to-date, comprehensive overview of the available evidence from randomized controlled trials regarding the possible benefits and harms of HFOV in preterm infants, they are unable to grasp the complexity of the clinical situation where substantial
variability exists in the characteristics of the patient, the ventilation strategies of HFOV and CV, and other neonatal supportive therapies. Hence, results of aggregate data meta-analyses are difficult to apply to the individual patient and therefore fail guiding neonatologists in their daily practice.

8.3 A systematic review with meta-analysis based on individual patient data (IPD).

To overcome the abovementioned limitations of aggregate data meta-analysis, we performed a meta-analysis based on the original individual patient data (IPD) from the randomized controlled trials. This methodology is relatively new\textsuperscript{28} and has never been applied in neonatal medicine before.

Generally speaking, IPD meta-analysis has a number of possible advantages over aggregate data meta-analysis.\textsuperscript{29,30} Specifically for our current case, the most important benefits of the IPD meta-analysis approach were the following:

1. We could collect previously unreported information at the level of the individual patient regarding the baseline risk profile of each infant (e.g. initial lung disease severity), the actually delivered mechanical ventilation to each infant (e.g. ventilator settings, partial carbon dioxide tensions, information on unreported outcomes, information at the level of the individual patient on ventilation strategies and surfactant therapy) and co-interventions administered to each infant (e.g. surfactant therapy, postnatal corticosteroids)
2. We could redefine outcomes uniformly across trials (e.g. for BPD) and new, composite outcomes (e.g. "death or BPD or adverse neurological event") could be generated.
3. It allowed doing analyses of subgroups of patients. Thus, for the first time it was possible to explore the relation between the infant’s risk profile and the treatment effect of HFOV.
4. It allowed exploring the importance of factors such as the timing of initiation of HFOV as effect modifier using information at the level of the individual infant.
5. It led to the formation of a pro-active, international collaborative research group consisting of all original trialists that a) defined the areas of clinical uncertainty, b) framed the scientific questions, c) co-designed the data analyses, d) provided the individual patient data of their trials, and e) reviewed and thoroughly discussed all results.

Our IPD meta-analysis also has limitations:

1. Of 7 out of the 17 eligible trials, IPD could not be collected. However, these 7 trials only included a total number of 430 infants, representing 11% of all infants ever randomized. This means that the IPD from almost 90% of all randomized infants has been collected, which is a relatively good result for an IPD meta-analysis as in 60% of IPD meta-analyses authors obtain data on less than 90% of all randomized patients (31). In addition, results from our IPD meta-analysis appeared robust to the inclusion or exclusion of aggregate data from the trials for which IPD were unavailable.
2. We used the “two-stage” approach in our IPD meta-analysis. Generally, two methodologies can be distinguished for IPD meta-analyses.\textsuperscript{31} In the “two-stage” approach effect estimates are first calculated for each trial separately and then combined using standard summary data meta-analysis techniques. In a “one-stage” approach IPD from all studies are combined to perform a single analysis, as if all patients belonged to a “mega-trial”. So far, the “two-stage” approach has been used most frequently in IPD meta-analyses (64%).\textsuperscript{31} It has the advantage that randomization is kept intact and that patients are only compared with patients from the same study. However, the "two-stage" approach has the disadvantage that
performing multiple subgroup analyses carries a risk of finding both false positive results (i.e. statistical significance by chance because of multiple testing) as well as false negative results (because of small number of infants in certain subgroups). Another disadvantage is the fact that it is a bi-variate analysis exploring only one other factor besides the treatment effect at a time. The “one-stage” approach is more flexible but requires careful clinical and statistical considerations in order to choose the most appropriate model. It has been used with success to explore the independent relation of several co-variates with clinical outcome and to make predictive models. However, if not stratified for trials, a “one-stage” analysis can be subject to bias.

3. Finally, a general disadvantage is that, compared with an aggregate data meta-analysis, an IPD meta-analysis takes a much greater effort in terms of time, human resources and costs. Thus, it will only be worthwhile doing it if obtaining the individual patient data will yield new, important information. Finding appropriate funding for this kind of research project is often a great challenge, especially because the methodology is largely unknown and often underestimated by reviewers of funding institutes.

8.4 What are the messages of the IPD meta-analysis for the practicing neonatologist?

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

2. 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.

3. 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.

4. 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.

8.5 Implications for future research

The following issues need further exploration:

1. The exact role of the timing of initiation of HFOV, i.e. with respect to the child’s time of birth or to the time since intubation, needs to be clarified. Also, the role 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 in modifying the observed treatment effect needs to be investigated. This can be done using existing data in a multivariate modelling approach.

2. More trials simply comparing the use of HFOV with CV in the early management of the preterm infant with respiratory failure are probably not useful. New trials regarding the use of HFOV should be focusing on the optimal timing of the first surfactant dose for infants ventilated with HFOV (i.e. before HFOV is started, immediately after HFOV
is started, or after alveolar recruitment with HFOV), or on what the role of HFOV can be as an adjunctive therapy to the non-invasive ventilatory management of respiratory distress syndrome (i.e. early nasal continuous positive airway pressure, followed by either HFOV or CV for infants failing nasal CPAP). In those trials, a lot of attention should go to the lung volume recruitment strategy of HFOV which should be aimed at recruiting lung volume optimally. Furthermore, HFOV should be compared with the most recent modes of CV, such as pressure support ventilation with volume guarantee, using strategies with limited tidal volumes and sufficient positive end expiratory pressure.

3. Our IPD meta-analysis has shown that international collaboration between neonatologists is possible and offers great opportunities to solve difficult, but important questions about the care of preterm infants in neonatal intensive care units. Particularly because in neonatal medicine large trials are so difficult to perform, collaboration between investigators over the world with similar interests is of great importance. We encountered a number of limitations which are related to the fact that our IPD meta-analysis was a retrospective study, such as the complete loss of trial data or the unavailability of certain information because of differences in trial protocol. In order to avoid these limitations, an IPD meta-analysis should be designed prospectively. One example is the NeOProM Collaboration, coordinated by Dr Lisa Askie, assessing appropriate levels of oxygen saturation for extremely preterm infants. Other topics such as non-invasive ventilatory support in the early management of respiratory distress syndrome, the management of post-haemorrhagic hydrocephalus or minimal surgery for necrotizing enterocolitis in extremely preterm infants could benefit from this approach.

8.6 References


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