Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients’ data


CRD summary
This high-quality review concluded that high-frequency oscillatory ventilation seemed equally effective as conventional ventilation in pre-term infants. The results did not support selection of pre-term infants for high-frequency oscillatory ventilation on the basis of gestational age, birth weight for gestation, initial lung disease severity or corticosteroid exposure. These conclusions reflected the evidence presented and are likely to be robust.

Authors' objectives
To assess the effectiveness of elective high-frequency oscillatory ventilation versus conventional ventilation in pre-term infants

Searching
Relevant trials were identified in a 2006 Cochrane Review (see Other Publications of Related Interest). MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Oxford Database of Perinatal Trials were searched, with no language restrictions, from 2006 to January 2009. Search terms were reported. Experts were also contacted to identify any published or unpublished trials.

Study selection
Eligible studies were randomised trials comparing high-frequency oscillatory ventilation to conventional ventilation in pre-term infants with respiratory insufficiency requiring mechanical ventilation. Pre-term infants were described as those less than 35 weeks gestational age. Treatment was considered elective if it was the main method of ventilation early in the course of treatment. Trials entering babies after conventional ventilation failed rescue were excluded.

Pre-specified primary outcomes were: death or bronchopulmonary dysplasia (defined as receipt of supplementary oxygen at 36 weeks postmenstrual age); death or severe brain injury (defined as grade three/four intraventricular haemorrhage, cystic periventricular leukomalacia, or both on ultrasound); and death or bronchopulmonary dysplasia at 36 weeks postmenstrual age or severe brain injury. In all trials, deaths were included up to discharge home of the infant. An additional 18 secondary outcomes were also investigated.

Single and multi-centre trials were included in the analysis using different modes of conventional ventilation (including intermittent positive pressure ventilation, synchronised intermittent mandatory ventilation and pressure support ventilation). Male infants represented over half of the participants in most of the trials; and the mean gestational age at birth ranged from 26 to 30 weeks.

Study selection was undertaken by two independent reviewers, with discrepancies resolved by consensus.

Assessment of study quality
Risk of bias was assessed through analysis of the adequacy of random sequence generation, allocation concealment, blinding of outcome assessment and completeness of follow-up data. Individual Patient Data (IPD) were checked for missing information, errors and inconsistencies with published aggregate data. All issues were referred to the trialists and corrected as necessary.

Validity assessment was undertaken by two independent reviewers, with discrepancies resolved by consensus.

Data extraction
Trial investigators provided IPD for central re-analysis.
Methods of synthesis
Two stage IPD meta-analysis was used to calculate overall treatment effects for multiple outcomes across ten trials and for a series of patient and trial level subgroups. Pre-specified subgroups were: gestation at delivery; birth weight for gestation; initial lung disease severity; antenatal treatment with corticosteroids, postnatal age, and period of exposure to conventional ventilation before initiation of high frequency oscillatory ventilation; ventilator type (SensorMedics 3100A, other oscillators, flow interrupters); and ventilation strategy (optimal lung volume strategy, lung protective ventilation strategy). Post-hoc subgroups were sex of infant, presence of chorioamnionitis and timing of first dose of exogenous surfactant.

Relative risk (RR) and associated 95% confidence intervals (CIs) were calculated for individual trials and pooled using both fixed-effect and random-effects models. Some secondary outcomes were continuous and effects were measured as weighted mean differences (WMDs). Heterogeneity was tested using $X^2$ and measured using $I^2$. Random-effects models were considered as sensitivity analyses and reported where $X^2$ was significant ($p<0.05$) or $I^2$ exceeded 50%. Interaction was tested for the subgroups. Analyses were based on intention-to-treat, and sensitivity analysis was used to explore the impact of the trial with more than 20% missing data and no blinding for brain ultrasound, trials with fewer than 100 patients, and trials with cross-over rates exceeding 20%.

Results of the review
Eighteen trials were eligible for inclusion (15 trials included in the Cochrane review, two subsequently published trials and one unpublished). IPD were available from ten trials ($n=3,229$). One trial of ten with available IPD had more than 20% missing data and assessment of brain ultrasound was not masked. Risk of bias is reported in the associated Cochrane Review (nine of ten trials were high quality, blinded, randomised controlled trials).

For infants ventilated with high-frequency oscillatory ventilation compared with conventional ventilation, the relative risk of death or bronchopulmonary dysplasia at 36 weeks post-menstrual age was 0.95 (95% CI 0.88 to 1.03); the relative risk of death or severe neurological event was 1.00 (95% CI 0.88 to 1.13), or the relative risk of any of these outcomes was 0.98 (95% CI 0.91 to 1.05). In addition to the non-significant pooled effects, there was no significant heterogeneity between trials for primary outcomes. Of secondary outcomes, only post-menstrual age (weeks) at final extubation differed from no effect (WMD 0.35 weeks, 95% CI -0.57 to -0.12), but this effect did not persist when a random-effects model was utilised ($I^2=46\%$).

Subgroups of infants did not benefit more or less from high-frequency oscillatory ventilation, including those based on gestation at delivery; birth weight for gestation; initial lung disease severity; antenatal treatment with corticosteroids, postnatal age, sex of infant, presence of chorioamnionitis and timing of first dose of exogenous surfactant; or intervention related subgroups (ventilator type and strategy). However, there was a benefit of high-frequency oscillatory ventilation for reduction of death, bronchopulmonary dysplasia or severe adverse neurological event where the period of conventional ventilation before high-frequency oscillatory ventilation was one to four hours (RR 0.82, 95% CI 0.72 to 0.94) with significant interaction ($p=0.014$).

Results of sensitivity analyses were robust in the exclusion of small trials, the exclusion of a trial with incomplete blinding and more than 20% missing data, and the exclusion of trials with a cross-over rate of 20% or more in at least one treatment group.

Authors' conclusions
High-frequency oscillatory ventilation seemed equally effective as conventional ventilation in pre-term infants. The results did not support selection of pre-term infants for high-frequency oscillatory ventilation on the basis of gestational age, birth weight for gestation, initial lung disease severity or exposure to corticosteroids.

CRD commentary
This high quality systematic review minimised potential bias using complementary and exhaustive search strategies, study selection based on inclusion criteria, validity assessment and data extraction, all applied by two independent reviewers. The analysis aimed to establish whether any types (subgroups) of pre-term infants might benefit from high-frequency oscillatory ventilation rather than conventional ventilation. An IPD approach (generally regarded as the gold
standard of systematic reviews) was used, resulting in standardisation in the definition of outcomes and subgroups, consistent analysis across trials and verification of data.

Appropriate two-stage analytical methods were used. The authors were explicit about the uncertainties surrounding the work; specifically, the large proportion of unavailable data, the high risk of false positive results from multiple comparisons, the risk of false negatives due to small sample sizes, and issues of blinding and missing data within trials. The multiple comparisons between the three (correlated) primary outcomes and subgroups result in a 43% chance of generating one or more significant results, such as the interaction associated with length of time period between conventional ventilation and high frequency oscillatory ventilation. Given the lack of significant relationships or dramatic effects, multiple testing was unlikely to have ramifications for conclusions regarding clinical practice.

Overall, the conclusions reflected the evidence presented and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future trials should compare high-frequency oscillatory ventilation with contemporary definitions of gentle ventilation during conventional ventilation. These trials should explore the optimum timing of surfactant administration and roles for high-frequency oscillatory ventilation in treatment of respiratory distress syndrome for subgroups such as infants who do not respond to initial non-invasive respiratory support. Future trials should also endeavour to hold data in long-term repositories and measure standardised metrics to facilitate future analysis. Further synthesis using a multivariate modelling approach is also warranted given the considerable complexity of analysis of multiple related outcomes and subgroups.

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