High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis

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CRD summary
This well-conducted review concluded that high frequency oscillation might reduce mortality in patients with acute respiratory distress syndrome compared with conventional ventilation and was unlikely to cause harm. These cautious conclusions were based on the results of the review and appear likely to be reliable.

Authors’ objectives
To compare the clinical and physiological effects of high frequency oscillation with those of conventional mechanical ventilation in patients with acute lung injury or acute respiratory distress syndrome (ARDS).

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched without language restrictions from inception to March 2010. Four relevant conference proceedings were searched from 1994 to 2010. Clinical experts were contacted and ClinicalTrials.gov and Current Controlled Trials were searched.

Study selection
Randomised controlled trials (RCTs) of high frequency oscillation compared with conventional mechanical ventilation in adults or children (aged at least four weeks and over 42 weeks from conception) with acute lung injury or ARDS who received conventional treatment were eligible for inclusion. Authors’ definitions of acute injury or ARDS were accepted.

Trials were required to report the primary outcome of hospital or 30-day mortality, or other clinical and physiological outcomes. Clinical outcomes included six-month mortality, duration of mechanical ventilation, ventilator-free days to day 28 or 30, health-related quality of life at one year and treatment failure (using the authors’ definitions) leading to crossover or discontinuation, or adverse events (including barotrauma, hypotension, obstruction of endotracheal tube from secretions and technical complications and equipment failure in patients treated with high frequency oscillation). Trials that also delivered a secondary intervention such as tracheal gas insufflation or recruitment maneuvers were included. Where the duration of high frequency oscillation was less than 24 hours, trials were included for the analyses of physiological outcomes but excluded from analyses of clinical outcomes. Where patients with other forms of respiratory failure were also included, a minimum of 70% of patients were required to have acute lung injury or ARDS. Crossover trials were excluded from the review.

All except one trial enrolled only patients with ARDS; the great majority of patients in the remaining trial also had ARDS. Two of the trials enrolled only children. Patients were enrolled either within 48 hours of diagnosis or up to five days after initiation of mechanical ventilation. The median baseline PaO\(_2\)/FiO\(_2\) ratio was 112 (range 80 to 122), where reported.

Two reviewers independently assessed studies for inclusion. Differences were resolved through discussion.

Assessment of study quality
Three reviewers independently assessed studies for validity using criteria of randomisation, allocation concealment, withdrawals and losses to follow-up, crossovers between groups, blinded outcome assessment and early stopping for benefit. Risk of bias was summarised using a modified form of the Cochrane Collaboration’s instrument for assessment of risk of bias. Standardisation of important cointerventions between treatment groups was assessed. Quality of evidence for each clinical outcome was rated using recommendations of the GRADE working group.

Data extraction
Data were extracted to permit the calculation of risk ratios (RR) with 95% confidence intervals (CI) using intention-to-treat principles where possible. Trial investigators were contacted to clarify methods or obtain additional data.

Three reviewers independently performed data extraction; disagreements were resolved through consensus.

**Methods of synthesis**
The trials were combined using random-effects meta-analyses to calculate pooled risk ratios with 95% CI. Statistical heterogeneity between studies was assessed using the $I^2$ statistic. A priori subgroup analyses were used to assess impacts of adult versus paediatric patients and high versus low risk of bias in trials. A post-hoc analysis was conducted to assess the primary outcome of mortality in trials mandating tidal volumes less than 8mL/kg of predicted or ideal body weight in the control group versus those that permitted higher tidal volumes. Publication bias was assessed by visual inspection of funnel plots and application of Begg's rank correlation test and a modified Macaskill's regression test.

**Results of the review**
Eight RCTs (n=431) were included in the review. Median sample size was 41 (range 16 to 148). Six trials were considered to be of high methodological quality. Risk of bias was unclear in the remaining two trials. All trials used concealed allocation and reported data permitting intention-to-treat analysis. Withdrawals and losses to follow-up were minimal.

High frequency oscillation significantly reduced mortality at discharge or 30 days (RR 0.77, 95% CI 0.61 to 0.98; six RCTs). There was no evidence of statistically significant heterogeneity ($I^2$=0%). There were no statistically significant differences in treatment effect in the subgroup analyses, including that of tidal volume in control groups. There was no evidence of publication bias.

There was a statistically significantly reduced rate of treatment failure (refractory hypoxaemia, hypercapnia, hypotension or barotrauma) in groups treated with high frequency oscillation (RR 0.67, 95% CI 0.46, 0.99; five RCTs) without significant heterogeneity ($I^2$=0%). There were no other statistically significant differences between treatment groups, including adverse events.

Analyses of physiological outcomes were also reported: increases in PaO$_2$/FiO$_2$ ratio of 16% to 24% relative to conventional mechanical ventilation and increased mean airway pressure by 22% to 33% at 24, 48, and 72 hours, but no effects on the oxygenation index and PaCO$_2$.

**Authors' conclusions**
High frequency oscillation might have reduced mortality in patients with ARDS compared with conventional ventilation and was unlikely to cause harm.

**CRD commentary**
The review question and the inclusion criteria were clear. The search was adequate. The lack of restrictions on publication status and language reduced the chances that relevant studies were omitted and bias introduced. The authors reported using rigorous methodology at all stages of the review process, which reduced chances of reviewer bias and error. Assessment of validity used appropriate criteria and was used to inform the synthesis. Use of meta-analysis was reasonable. Appropriate assessment and exploration of heterogeneity between studies was undertaken. The authors’ cautious conclusions were based on the results of the review and appear likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated clinicians who use or are considering use of high frequency oscillation to treat ARDS can be reassured by the results of this review, which indicate that it is a safe and effective alternative to conventional ventilation, at least in centres proficient in its use.

**Research:** The authors noted that two ongoing trials will enrol more than 2,000 patients and address insufficiencies in current data.
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