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High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term (Review)

De Paoli AG, Clark RH, Bhuta T, Henderson-Smart DJ

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[Intervention Review]

High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term

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ABSTRACT

Background

Pulmonary disease is a major cause of mortality and morbidity in term and near term infants. Conventional ventilation (CV) has been used for many years but may lead to lung injury, require the subsequent use of more invasive treatment such as extracorporeal membrane oxygenation (ECMO), or result in death. There are some observational studies indicating that high frequency oscillatory ventilation (HFOV) may be more effective in these infants as compared to CV.

Objectives

To determine the effect of HFOV as compared with CV on mortality and morbidity in infants born at 35 weeks gestational age or more with severe respiratory failure requiring mechanical ventilation.

Search methods

Standard search methods of the Cochrane Neonatal Review group were used. These included searches in January 2009 of The Cochrane Library, MEDLINE, EMBASE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, and journal hand searching by the Cochrane Collaboration.

Selection criteria

Randomized or quasi-randomized trials comparing HFOV and CV in term or near term infants with intractable respiratory failure were included in this review.

Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group were used. The investigators separately extracted, assessed and coded all data for each study. Any disagreement was resolved by discussion. Data were synthesized using risk ratio [RR with (95% confidence intervals, CI)] and mean difference (with standard deviation, SD).

Main results

Two trials met the inclusion criteria. One trial involving the "elective" use of HFOV randomized 118 infants at the start of CV. The other trial of "rescue" HFOV randomized 81 infants with later respiratory failure on CV. Neither trial showed evidence of a reduction in mortality at 28 days or in failed therapy on the assigned mode of ventilation requiring cross-over to the other mode. Neither study reported significant

differences in the risk of pulmonary air leak, chronic lung disease (28 days or more in oxygen) or intracranial injury. In the study of elective HFOV, there was no difference noted in days on a ventilator or days in hospital. In the one rescue study, there was no difference in the risk of needing extracorporeal membrane oxygenation.

Authors' conclusions

There are no data from randomized controlled trials supporting the use of rescue HFOV in term or near term infants with severe pulmonary dysfunction. The area is complicated by diverse pathology in such infants and by the occurrence of other interventions (surfactant, inhaled nitric oxide, inotropes). Randomized controlled trials are needed to establish the role of elective or rescue HFOV in near term and term infants with pulmonary dysfunction before widespread use of this mode of ventilation in such infants.

PLAIN LANGUAGE SUMMARY

High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term

In babies born at or near term (over 34 weeks gestation) who have severe respiratory failure due to lung disease, there is no evidence from randomized controlled trials to suggest that the use of high frequency oscillatory ventilation is better than conventional mechanical ventilation.

All infant outcomes were similar in the two treatment groups.

BACKGROUND

Pulmonary disease is a major cause of mortality and morbidity in term and near term newborn infants (35 or more weeks of gestation at birth). The most frequent serious pulmonary disorders are meconium aspiration, pneumonia, respiratory distress syndrome (RDS), persistent pulmonary hypertension and diaphragmatic hernia.

Intermittent positive pressure ventilation (IPPV) is used for severe respiratory failure in about 0.3% of term infants. Conventional ventilation (CV) is administered with a time-cycled pressure-limited or volume-targeted ventilator providing rates usually in the range of 30 - 80 breaths per minute. This form of IPPV, together with exposure to high toxic levels of oxygen, is thought to lead to lung injury and pulmonary morbidity (Clark 2000a). In some infants, CV fails to maintain adequate gas exchange and they either die or are treated with extracorporeal membrane oxygenation (ECMO), a more invasive treatment.

Observational studies have suggested that high frequency oscillatory ventilation (HFOV) is an effective method of providing pulmonary gas exchange in animals with severe pulmonary disease (Truog 1984; deLemos 1987; Gerstmann 1988) and may also reduce the severity of lung injury induced by mechanical ventilation. HFOV involves provision of an oscillatory wave form at about 10 Hz, where mean airway pressure determines lung volume leading to oxygen transfer and the amplitude of oscillation determines carbon dioxide exchange. The waveform is generated by specialized piston oscillators, flow interrupters or diaphragms.

HFOV has been used for the mechanical ventilation of preterm infants born at less than 35 weeks gestation who have respiratory distress syndrome (RDS). It has been used electively from the onset of mechanical ventilation (Henderson-Smart 2007) or as rescue therapy when conventional ventilation fails (Bhuta 1998).

Uncontrolled rescue studies in term infants (Kohlet 1988; Carter 1990) indicate that HFOV might be of value in neonates with intractable respiratory failure who are candidates for ECMO. In the case series of Carter et al (Carter 1990) fifty term or near term infants were admitted for ECMO. All infants had a PAO_2 - PaO_2 gradient greater than or equal to 600 mmHg in spite of aggressive conventional ventilatory and pharmacological therapy. All patients were offered HFOV and, if no improvement occurred, were treated with ECMO. Forty-six of the patients were treated with a staged protocol using HFOV before ECMO. Twenty-one of these 46 (46%) responded to HFOV treatment alone and did not require ECMO therapy. There were no statistically significant differences in outcomes with respect to number of ventilator days, hospital days, or survival between patients responding to HFOV and patients who received ECMO. However, morbidity was increased in ECMO patients. Bleeding abnormalities, seizures, and renal failure occurred more frequently than in HFOV treated infants.

This review examines the results of randomized controlled trials of elective and rescue HFOV versus CV in term or near term infants with respiratory failure requiring mechanical ventilation.

OBJECTIVES

To determine the effect of HFOV as compared with CV on mortality and morbidity in infants born at 35 weeks or more gestational age

with severe respiratory failure requiring mechanical ventilation due to lung disease.

Comparisons:

1. Elective HFOV versus conventional ventilation
2. Rescue HFOV versus conventional ventilation

Prespecified subgroup analyses.

1. Trials with and without surfactant replacement therapy. Surfactant therapy would increase alveolar recruitment and may be beneficial when used in conjunction with HFOV.
2. Trials with and without high lung volume HFOV strategies. These include the use of higher mean airway pressures, maneuvers to re-inflate the lung after suctioning and weaning of inspired oxygen before pressures.
3. Trials using different ventilators to deliver HFOV.
4. Trials of Infants with different lung pathology. These include meconium aspiration, pneumonia, respiratory distress syndrome (RDS), persistent pulmonary hypertension and diaphragmatic hernia.
5. Trials with and without the use of inhaled nitric oxide in conjunction with HFOV or CV.
6. Trials in which CV was pressure limited or volume limited.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials.

Types of participants

- Infants at term or near term (35 or more weeks gestational age)
- Elective HFOV: severe pulmonary dysfunction (such as hypoxemia despite the use of high inspired oxygen, hypercarbia) leading to initial CV
- Rescue HFOV: severe pulmonary dysfunction on conventional mechanical ventilation

Types of interventions

HFOV vs. CV.

HFOV was defined as ventilation with rates of about 10 - 20 Hz, a fractional inspiratory time of 0.3 and a pressure amplitude sufficient to produce visible chest wall motion.

CV was defined as time-cycled and pressure or volume-limited IPPV with rates less than 120/min.

Types of outcome measures

Primary:

- 1) Mortality at 28 - 30 days, at discharge and in the first year
- 2) Failed therapy on assigned mode of ventilation

Secondary:

- 3) Use of ECMO

4) Evidence of brain pathology on ultrasound, computerized tomography or other imaging (intraventricular or intracerebral hemorrhage, intraventricular leukomalacia, cysts, or cerebral atrophy)

5) Pulmonary air leak syndromes

Any pulmonary air leak

Gross pulmonary air leak (extra-pulmonary such as pneumothorax)

6) Chronic lung disease (CLD) - supplemental oxygen at 28 - 30 days or at discharge home

7) Duration of mechanical ventilation (days)

8) Days in hospital and costs

9) Respiratory illness or failure (physician attendance or hospital admissions) in the first year or in later childhood

10) Sensory (hearing and vision), motor and mental development in childhood

Search methods for identification of studies

Searches were done for randomized studies listed in MEDLINE by means of the MeSH terms 'high frequency ventilation', 'high frequency oscillatory ventilation', 'oscillatory ventilation' and 'infant, newborn', from the years 1980 to January 2009. The EMBASE database (1982 to January 2009), the Oxford Database of Perinatal Trials and the Cochrane Central Register of Controlled Trials (Central), The Cochrane Library, Issue 4 2008, were similarly searched. Information was obtained from experts in the field and also cross references were checked. Proceedings of recent meetings of the American Society for Pediatric Research and the European Society for Pediatric Research from 1995 to 2008 were searched for new studies that have not been published in full.

Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group were used. This included independent assessment of study eligibility and quality by each review author.

Methods used to collect data from the included trials:

Each author extracted data separately and then compared and resolved any differences.

Methods used to analyse the data:

The standard method of the Cochrane Neonatal Review Group using relative ratio (RR) with 95% confidence intervals in brackets after RR. Also mean differences with standard deviation (SD) in brackets.

RESULTS

Description of studies

Two eligible trials were found (Clark 1994, Rojas 2005).

Elective HFOV

The Rojas 2005 trial included infants (118) born at greater than 35 weeks gestational age and with birth weight of 1750 grams or more. They were 4 - 48 hrs of age and had respiratory failure (requiring 60% or more oxygen to maintain oxygen saturation greater than 90% and PaO₂ 60 mmHg or more) with intent to

introduce mechanical ventilation. They were briefly started initially on CV with a mean airway pressure of 9 cmH₂O and average inspired oxygen of 80% and were expected to require more than 24 hours of mechanical ventilation. Randomization was done at less than 8hrs of CV to elective use of HFOV compared with continued CV.

Interventions included HFOV - Sensormedics ventilators - using mean airway pressure 2 cm H₂O above that on CV before enrolment, inspiratory/expiratory ratio of 0.33, rate 10 Hz and the main method to improve oxygenation was to increase the mean airway pressure. Hypoxemia on CV was adjusted by modifying FiO₂ when this was less than 0.40 or modifying peak and/or end expiratory pressure when FiO₂ was greater than 0.40. Carbon dioxide levels were modified by changing the peak inspiratory pressure or ventilator rate (not more than 80 breaths per minute).

Rescue HFOV

The Clark 1994 trial recruited patients between 1990 - 92. Neonates were eligible for the rescue study if their estimated gestational age was greater than 34 weeks, their birth weight was equal to or greater than 2 kg, they were less than 14 days of age and, on conventional mechanical ventilation, their FiO₂ requirements were greater than 0.5, mean airway pressure was greater than 10cm H₂O, peak inspiratory pressure greater than 30 cm H₂O and respiratory rate greater than 40/min.

If the partial pressure of oxygen was less than 35 mm Hg on three arterial blood gas studies, or if the infants presented in profound shock or needed cardiopulmonary resuscitation, they were eligible for immediate ECMO and were excluded from enrolment on that basis. Eighty one patients were randomized to HFOV or CV. Twenty-two per cent of the patients had received surfactant prior to trial entry.

HFOV was carried out with Sensormedics 3100 set at a frequency of 10 Hz, a fractional inspiratory time of 0.33 and a pressure amplitude sufficient to produce visible chest wall motion. The initial mean airway pressure was set at 1 - 2 cm higher than CV.

CV was provided with pressure limited, time-cycled ventilators. The target range for PCO₂ was 25 to 35 mm Hg in patients with pulmonary hypertension and in all other patients it was 45 to 55 mmHg.

Treatment Failure: Patients who failed to respond to the assigned mode of ventilation were crossed over to the alternative mode of ventilation. The criteria for treatment failure were

- 1) PaO₂ less than 65 mm Hg on an FiO₂ of 1.0 for 2 hours
- 2) PaO₂ below the target range for 2 hours
- 3) air leak that was severe (more than two chest tubes) or persistent (more than 24 hours)
- 4) cardiac impairment on the ventilator settings required to achieve adequate gas exchange

ECMO criteria: To be considered for ECMO the neonate had to have reversible lung disease and have no evidence of intracranial haemorrhage or coagulopathy. In addition, the neonate had to have one of the following signs of respiratory failure:

- 1) alveolar-arterial oxygen difference greater than 610 mmHg for eight hours

- 2) alveolar-arterial oxygen difference greater than 605 mmHg and peak pressure of at least 38 cmH₂O for four hours
- 3) oxygenation index greater than 40 on three of five post-ductal gases obtained at least 30 minutes apart
- 4) severe, refractory respiratory failure with sudden decompensation despite maximum medical management for two hours

Risk of bias in included studies

In [Rojas 2005](#) randomization was concealed (sealed opaque envelopes), stratified by cause of respiratory failure (respiratory distress syndrome, pulmonary sepsis, meconium aspiration, persistent pulmonary hypertension). Interventions were not blinded and no evidence was given regarding blinding of outcome assessments.

In [Clark 1994](#) the subjects were stratified before randomization on the basis of their primary admission diagnosis. These were pneumonia, hyaline membrane disease, meconium aspiration syndrome, air leak or other. Randomization was blinded. Two infants, one from each group were excluded after randomization because of congenital abnormalities. One had total anomalous pulmonary venous return and one had Jeune syndrome. Outcomes were assessed blinded to group assignment for head ultrasounds and diagnosis of CLD, but not for pulmonary air leaks.

Effects of interventions

There were two trials included in this review (118 elective HFOV [Rojas 2005](#) and 79 rescue HFOV [Clark 1994](#)). The trials did not show any significant differences in any outcomes between the HFOV and CV groups.

HFOV vs. CV in term or near term infants (Comparison 1)

Mortality at 28 days (Outcome 1.1):

Mortality at 28 days was similar in the combined result from the two trials. There was no difference in mortality in the individual trials that examined elective HFOV [[Rojas 2005](#); HFOV 5/54, CV 1/64; RR 5.93 (95%CI, 0.71, 49.19)] and rescue HFOV [[Clark 1994](#); HFOV 1/39, CV 2/40; RR 0.51 (95%CI, 0.05, 5.43)].

Failed therapy on assigned mode of ventilation (Outcome 1.2):

Failed therapy on assigned mode of ventilation was reported by both trials ([Clark 1994](#), [Rojas 2005](#)). The rates in the elective HFOV trial ([Rojas 2005](#)) were 4/54 in HFOV and 0/64 in CV [RR 10.64 (95%CI, 0.59, 193.23)] and in the rescue trial ([Clark 1994](#)) 17/39 on HFOV and 24/40 on CV [RR 0.73 (95%CI, 0.47, 1.13)].

Received ECMO (Outcome 1.3):

Patients receiving ECMO was reported in the rescue trial ([Clark 1994](#)). There was a trend towards an increase in the number of infants requiring ECMO in the HFOV group (12/39) compared with the CV group (6/40); however, this was not statistically significant [RR 2.05 (95%CI, 0.86, 4.92)].

Intracranial Hemorrhage (Outcome 1.4):

The definition of intracranial hemorrhage varied between the two trials. In the [Clark 1994](#) rescue HFOV trial the rates of any intracranial hemorrhage by 28 days or discharge were not

significantly different [RR 0.51 (95%CI, 0.05, 6.08)]. In the [Rojas 2005](#) elective HFOV trial the rates of grades three or four intraventricular hemorrhage were similar in the treatment groups [RR 0.57 (95%CI, 0.05, 6.08)].

Pulmonary Airleak (Outcome 1.5):

Pulmonary air leak was reported in both trials ([Clark 1994](#), [Rojas 2005](#)). In the elective HFOV trial ([Rojas 2005](#)) rates were 2/64 on HFOV and 1/64 on CV [RR 2.37 (95%CI, 0.22, 25.43)]. In the rescue trial ([Clark 1994](#)) rates were 4/39 on HFOV and 6/40 on CV [RR 0.68 (95%CI, 0.21, 2.24)].

Chronic lung disease at 28 days (Outcome 1.6):

Chronic lung disease (CLD) was reported in the two trials ([Clark 1994](#), [Rojas 2005](#)), with the same definition of supplemental oxygen at 28 days. In the elective trial ([Rojas 2005](#)) rates were 23/49 on HFOV and 26/63 on CV [RR 1.14 (0.75, 1.73)]. In the rescue trial ([Clark 1994](#)) rates were 11/39 on HFOV and 5/40 on CV [RR 2.26 (95%CI, 0.86, 5.9)].

Periventricular leukomalacia (Outcome 1.7):

Periventricular leukomalacia (PVL) was reported by [Rojas 2005](#) in the elective trial and occurred at similar rates in the two treatment groups [2/52 on HFOV and 0/59 on CV; RR 5.66 (0.28, 115.27)].

Days on mechanical ventilation (Outcome 1.8):

The mean days on mechanical ventilation were reported by [Rojas 2005](#) and was similar in the two groups [mean difference 0.70 (SD -0.97, 2.37)]. [Clark 1994](#) reported similar median (and range) of days on ventilators for all subjects, 8 (3-36) in the HFOV group and 8 (2-28) in the CV group.

Days of hospitalisation (Outcome 1.9):

The duration of hospitalisation was similar in the two treatment groups. [Rojas 2005](#) found mean days of 18.0 (SD 10.1) on HFOV and 20 (SD 12.4) on CV; [mean difference -2.00 (SD -6.17, 2.17)]. [Clark 1994](#) reported median (range) of days with 22 (7 - 83) on HFOV and 21 (9 - 124) on CV, which were similar.

No other pre-specified outcomes were reported in these studies. Importantly, there were no post discharge data on infant respiratory function and care, and on long term growth and neuro-development.

DISCUSSION

Two trials were identified that addressed the issue of HFOV compared to conventional ventilation in term or near term infants with respiratory failure. [Clark 1994](#) directed the use of the alternative treatment if prespecified failure criteria were met, thus leading to underestimation of any real treatment effects. The sample size required for this trial was 250 patients. However, due to difficulty in enrolling patients because of increasing use of HFOV by the referral centres, the trial was prematurely terminated when only 81 patients had been randomized. Thus, this trial did not have adequate power to detect significant differences in outcome.

Elective and rescue HFOV is also used in preterm infants to prevent death and morbidity including chronic lung disease and is the subject of others' reviews ([Henderson-Smart 2007](#); [Bhuta 1998](#)).

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. There may be a small reduction in the rate of CLD (oxygen therapy required at 36 weeks postmenstrual age) with HFOV use, but the evidence is weakened by the inconsistency of this effect across trials and the overall borderline significance. There is insufficient information on the use of rescue HFOV to make recommendations for practice. The small amount of data that exists suggest that harm might outweigh any benefit.

A recent report of the ECMO Life Support Organization (ELSO) Registry shows that high frequency ventilation is being commonly used before rescue treatment with ECMO (Roy 2000). Additionally, studies of inhaled nitric oxide have suggested that HFOV is important as a lung recruitment tool (Clark 2000b). There is increasing clinical use of HFOV in rescuing infants with respiratory failure.

However, since the early observational studies and the two randomized studies included in this review showing no significant effect on outcomes, there have been important changes in the practice of neonatal medicine including increasing use of surfactant, nitric oxide and other interventions such as inotropic agents. As described by Jaballah 2006 in his observational study on the background of changing practices, it is difficult to tease out confounders and so it is vitally important that randomized controlled trials be done to establish the place of HFOV in these groups of patients.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomized controlled trial data supporting the use of rescue or elective use of HFOV compared with CV in term or near term infants with severe respiratory failure due to pulmonary disease.

Implications for research

In view of the increasing use of HFOV in practice, randomized controlled trials are urgently needed to establish its role for elective use and for rescue use in term or near term infants with severe pulmonary disease. The randomization should be stratified by disease and long- term outcomes should be reported.

ACKNOWLEDGEMENTS

Dr RH Clark kindly provided additional data regarding his study in terms of blinding of randomization and blinding of outcomes.

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References to studies included in this review

Clark 1994 {published data only}

Clark RH, Yoder BA, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. *Journal of Pediatrics* 1994;**124**:447-54.

Rojas 2005 {published data only}

Rojas MA, Lozano JM, Rojas MX, Bose CL, Ronon MA, Ruiz G, Pineros JG, Rojas C, Robayo G, Hoyos A, Celis LA, Torres S, Correa J, Colombian Neonatal Research Network. Randomized, multicentre trial of conventional ventilation versus high-frequency oscillatory ventilation for the early management of respiratory failure in term or near-term infants in Colombia. *Journal of Perinatology* 2005;**25**:720-4.

References to studies excluded from this review

Kinsella 1997 {published data only}

Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension of the newborn. *Journal of Pediatrics* 1997;**131**:55-62.

Additional references

Bhuta 1998

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Carter 1990

Carter JM, Gerstmann DR, Clark RH. High frequency oscillation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. *Pediatrics* 1990;**85**:159-64.

Clark 2000a

Clark RH, Slutsky AS, Gerstmann DR. Lung protection strategies for ventilation in the neonate: What are they?. *Pediatrics* 2000;**105**:112-114.

Clark 2000b

Clark RH, Keuser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, Roy BJ, Keszler M, Kinsella JP, for the Clinical Inhaled Nitric Oxide Research Group. Low dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *New England Journal of Medicine* 2000;**342**:469-74.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

deLemos 1987

deLemos RA, Coalson JJ, Gerstmann DR, et al. Ventilatory management of infant baboons with hyaline membrane disease; the use of high frequency ventilation. *Pediatric Research* 1987;**21**:594-602.

Gerstmann 1988

Gerstmann DR, deLemos RA, Coalson JJ, et al. Influence of ventilatory technique on pulmonary baroinjury in baboons with hyaline membrane disease. *Pediatric Pulmonology* 1988;**5**:82-91.

Henderson-Smart 2007

Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: [10.1002/14651858.CD000104.pub2](https://doi.org/10.1002/14651858.CD000104.pub2)]

Jaballah 2006

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Kohlet 1988

Kohlet D, Perlman M, Kirpalani H. High frequency oscillation in the rescue of infants with persistent pulmonary hypertension. *Critical Care Medicine* 1988;**16**:510-6.

Roy 2000

Roy BJ, Rycus P, Conrad SA, Clark RH. The changing demographics of neonatal ECMO patients reported to the ELSO Registry. *Pediatrics* 2000;**106**:1334-1338.

Truog 1984

Truog WE, Standaert TA, Murphy JH, Woodrum DE, Hodson WA. Effects of prolonged high frequency oscillatory ventilation in premature primates with experimental hyaline membrane disease. *American Review of Respiratory Diseases* 1984;**130**:76-80.

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Bhutta 2001

Bhuta T, Clark RH, Henderson-Smart DJ. Rescue high frequency oscillatory ventilation vs conventional ventilation for infants with severe pulmonary dysfunction born at or near term. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [DOI: [10.1002/14651858.CD002974](https://doi.org/10.1002/14651858.CD002974)]

Clark 1994

Methods	Multicentre randomised controlled trial. 4 centres. The subjects were stratified according to the admission diagnosis and then randomized. Randomization was blinded. The intervention for obvious reasons could not be blinded. Completeness of follow up: 2 patients were excluded after randomization. The outcomes of head ultrasound and CLD were blinded, however the air leak outcome was not blinded.
Participants	Eighty one infants greater than 34 weeks gestation, birthweight equal or greater than 2 kg, less than 14 days of age and requiring > 0.5 FiO_2 and mean airway pressure > 10 cms were eligible for the trial. Entry measures were; median age 29 days (range 2-149), similar mean FiO_2 of 0.95 in HFOV group and 0.97 in CV group, higher peak inspiratory pressure (cm H_2O , $P<0.05$) in HFOV group (mean 39, SD 8) and CV group (mean 34, SD 5), mean airway pressure (cm H_2O) were similar in the two groups (HFOV 17, CV 16), more already met ECMO criteria in the HFOV group (26) compared with the CV group (16) ($P<0.05$)
Interventions	HFOV. High volume strategy was used, thus oxygen was weaned before mean airway pressure. Frequency was set at 10Hz, pressure amplitude sufficient to produce visible chest motion. CV consisted of time cycled pressure limited IPPV with rates less than 120/min. The goal was to use the lowest possible peak pressures to avoid lung barotrauma. In patients with alkalosis-responsive pulmonary hypertension, the target partial pressure of arterial carbon dioxide was 25 to 35 mm Hg. In other patients it was 45 to 55 mm Hg.
Outcomes	Mortality at 28 days, failed treatment requiring crossover, use of ECMO, CLD at 28 days of age, numbers of days in hospital, on ventilator and on oxygen.
Notes	Trial specified use of the alternate treatment following failure of assigned mode of ventilation. Additional information regarding the blinding of randomization and of the outcome of head ultrasound were provided by Dr RH Clark.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Rojas 2005

Methods	<p>Blinding of randomization - yes (sealed opaque envelopes)</p> <p>Randomisation stratified by cause of respiratory failure (respiratory distress syndrome, pulmonary sepsis, meconium aspiration, persistent pulmonary hypertension).</p> <p>Blinding of intervention - no</p> <p>Completeness of follow up - yes</p> <p>Blinding of out outcome assessments - no</p> <p>Multicentre trial in 5 neonatal intensive care units.</p>
Participants	<p>Infants (118) born at greater than 35 weeks gestational age and with birth weights of 1750 grams or more. They were 4 - 48 hrs of age and had respiratory failure (requiring 60% or more oxygen to maintain oxygen saturation over 90% and PaO_2 60 mmHg or more) with intent to introduce mechanical ventilation. They were briefly started initially on CV and entered the trial within 8 hrs, with mean airway pressure of 9 cms H_2O and average inspired oxygen of 80%. At the time of randomization measurements of ventilatory support were similar in the two groups.</p> <p>Exclusion criteria - major congenital abnormality, multiple birth, presence of pulmonary air leak.</p>

Rojas 2005 (Continued)

Interventions	HFOV - Sensormedics ventilators - using mean airway pressure 2 cm H ₂ O above that on CV before enrolment, inspiratory/expiratory ratio of 0.33, rate 10 Hz, main method to improve oxygen level was pressure increase.	
Outcomes	Neonatal death, pulmonary air leak, failed mechanical ventilation, duration of mechanical ventilation, chronic lung disease (need supplemental oxygen at 28 days), grade 3 and 4 intraventricular hemorrhage, periventricular leukomalacia, length of hospitalisation.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Opaque sealed envelopes

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Kinsella 1997	This study was a randomised controlled trial comparing inhaled nitric oxide with high frequency oscillatory ventilation in severe pulmonary hypertension of the newborn.

DATA AND ANALYSES
Comparison 1. HFOV vs CV in term or near term infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 28 days	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Elective HFOV	1	118	Risk Ratio (M-H, Fixed, 95% CI)	5.93 [0.71, 49.19]
1.2 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.43]
2 Failed therapy on assigned mode of ventilation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Elective HFOV	1	118	Risk Ratio (M-H, Fixed, 95% CI)	10.64 [0.59, 193.23]
2.2 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.13]
3 Received ECMO	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.86, 4.92]
4 Intracranial hemorrhage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Elective HFOV	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.05, 6.08]
4.2 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.43]
5 Pulmonary air leak	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Elective HFOV	1	118	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.22, 25.43]
5.2 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.21, 2.24]
6 Chronic lung disease at 28 days	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Elective HFOV	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.75, 1.73]
6.2 Rescue HFOV	1	79	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.86, 5.90]
7 Periventricular leukomalacia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Elective HFOV	1	111	Risk Ratio (M-H, Fixed, 95% CI)	5.66 [0.28, 115.27]
8 Days of mechanical ventilation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Elective HFOV	1	112	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.97, 2.37]
9 Days of hospitalisation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Elective HFOV	1	112	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-6.17, 2.17]

Analysis 1.1. Comparison 1 HFOV vs CV in term or near term infants, Outcome 1 Death at 28 days.

Analysis 1.2. Comparison 1 HFOV vs CV in term or near term infants, Outcome 2 Failed therapy on assigned mode of ventilation.

Analysis 1.3. Comparison 1 HFOV vs CV in term or near term infants, Outcome 3 Received ECMO.

Analysis 1.4. Comparison 1 HFOV vs CV in term or near term infants, Outcome 4 Intracranial hemorrhage.

Analysis 1.5. Comparison 1 HFOV vs CV in term or near term infants, Outcome 5 Pulmonary air leak.

Analysis 1.6. Comparison 1 HFOV vs CV in term or near term infants, Outcome 6 Chronic lung disease at 28 days.

Analysis 1.7. Comparison 1 HFOV vs CV in term or near term infants, Outcome 7 Periventricular leukomalacia.

Analysis 1.8. Comparison 1 HFOV vs CV in term or near term infants, Outcome 8 Days of mechanical ventilation.

Analysis 1.9. Comparison 1 HFOV vs CV in term or near term infants, Outcome 9 Days of hospitalisation.

WHAT'S NEW

Date	Event	Description
25 February 2013	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 1, 2001

Date	Event	Description
7 December 2010	Amended	Contact details updated.
12 August 2009	Amended	Minor text edits per author request.
12 May 2009	New search has been performed	This updates the review "Rescue high frequency oscillatory ventilation vs conventional ventilation for infants with severe pul-

Date	Event	Description
		monary dysfunction born at or near" published in The Cochrane Library, Issue 1 2001 (Bhutta 2001).
		The definition of severe respiratory failure in eligible trial participants was previously based only on infants with respiratory failure on conventional ventilation (rescue), but has now been broadened to include infants with respiratory failure requiring mechanical ventilation who are then electively randomized to receive HFOV or CV.
12 May 2009	New citation required but conclusions have not changed	New authorship.
16 May 2008	Amended	Converted to new review format.
13 November 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Tushar Bhuta, David Henderson-Smart and Reese Clark independently assessed the studies and extracted the data for the initial review.

Tushar Bhuta and David Henderson-Smart prepared the manuscript.

David Henderson-Smart undertook the current major revision and update with the help of Tony De Paoli. Reese Clark and Tushar Bhuta agreed with the inclusion of a new trial and the broadening of the review to include both elective and rescue use of HFOV.

DECLARATIONS OF INTEREST

Reese Clark is an author of one of the included studies.

SOURCES OF SUPPORT

Internal sources

- Pediatrix Medical Group, Ft Lauderdale, Florida, USA.
- Centre for Perinatal Health Services Research, University of Sydney, Australia.
- Royal North Shore Hospital, Sydney, Australia.
- Royal Hobart Hospital, Hobart, Tasmania, Australia.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

High-Frequency Ventilation [*methods] [mortality]; Lung Diseases [*therapy]; Randomized Controlled Trials as Topic; Respiration, Artificial [methods]; Salvage Therapy; Term Birth; Treatment Outcome

MeSH check words

Humans; Infant, Newborn