

A randomised controlled trial and cost-effectiveness analysis of high-frequency oscillatory ventilation against conventional artificial ventilation for adults with acute respiratory distress syndrome. The OSCAR (OSCillation in ARDS) study

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Scientific summary

The OSCAR (OSCillation in ARDS) study

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Scientific summary

Background

The acute respiratory distress syndrome (ARDS) is a general term covering most causes of acute, severe type 1 (hypoxaemic) respiratory failure. Most patients with ARDS will require a period of artificial ventilation on an intensive care unit (ICU) if they are to survive. Although reasonably uncommon in population terms, the treatment of ARDS is very resource intensive and comprises a substantial proportion of the workload of most ICUs.

While initially life saving, artificial ventilation using conventional techniques can further injure the patient's lungs and perpetuate, rather than cure, the lung inflammation that is the hallmark of ARDS. The mortality attributed to artificial ventilation, over and above the underlying disease, may be 8% or more.

High-frequency oscillatory ventilation (HFOV) is a form of artificial ventilation first used on premature infants, where very small breaths are given very frequently (up to 10 times a second) while the patient's lungs are kept in a partly inflated state. This is believed to reduce the mechanical trauma to the lungs that causes the continued inflammation. A number of small studies in adults with ARDS, when combined in a meta-analysis, suggested that there might be a survival advantage if HFOV was used in place of conventional artificial ventilation. This, coupled with the increasing use of HFOV in the NHS, led the Health Technology Assessment programme to commission an effectiveness study comparing HFOV with conventional artificial ventilation in patients with ARDS, the OSCAR (OSCillation in ARDS) study, using mortality as the primary outcome.

Objectives

The primary research objective was to determine the effect of HFOV on all-cause mortality 30 days after randomisation in patients receiving artificial ventilation for acute, severe type 1 respiratory failure compared with conventional artificial ventilation.

Secondary research objectives included determining the effects of HFOV on survival at hospital discharge and later, on non-pulmonary organ failures while treated on an ICU, on health-related quality of life 6 months and 1 year after randomisation, on self-reported respiratory function, and on resource use in the ICU.

The economic analysis research objectives were to determine the health-care system benefit of HFOV measured as the cost per quality-adjusted life-year (QALY) gained 1 year after randomisation, and to determine the effect of HFOV on the utilisation of hospital and community care resources after acute hospital discharge 1 year after randomisation.

Methods

The study was an unblinded, randomised clinical trial of HFOV compared with usual ventilatory care in patients with severe type 1 respiratory failure. Patients were eligible for the study if they were ≥ 16 years of age, weighed 35 kg or more, were receiving artificial ventilation via an endotracheal or tracheostomy tube, and had acute hypoxaemic respiratory failure as defined by:

- lowest recorded partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen (P : F) ratio measured between onset of artificial ventilation and time of screening of ≤ 26.7 kPa with a positive end expiratory pressure ≥ 5 cmH₂O
- bilateral infiltrates on chest radiograph.

The patients had to be expected to require artificial ventilation until at least the evening of the day after enrolment (predicted by attending clinician) and had to have been artificially ventilated for < 7 consecutive days (≤ 168 hours) at the point of randomisation.

Patients ineligible for the study included those with respiratory failure attributable to left atrial hypertension from any cause, diagnosed clinically or with echocardiography or pulmonary artery catheterisation, and those in whom HFOV would be contraindicated, including patients with moderate or severe airway disease expected to cause expiratory airflow limitation. Patients enrolled in another therapeutic trial in the 30 days prior to randomisation were excluded. Patient consent, or, more commonly, consent/assent obtained from personal or nominated professional consultees in England and Wales, or welfare guardians/nearest relatives in Scotland, was required before enrolment.

The intervention was HFOV started after randomisation and continued until the patients had recovered sufficiently to be weaned from artificial ventilation, when their FiO_2 was 0.4 or less, and when the local clinician is satisfied that there are no non-pulmonary impediments to weaning. The study sites all used the Novalung R100® ventilator (Metran Co. Ltd, Saitama, Japan) for HFOV. The control group of patients received usual ventilator care for the study site.

The economic evaluation was carried out alongside the trial using recommended methods. An additional model-based analysis was used to extrapolate the results over the expected lifetime of the trial participants. The perspective of the NHS and personal social services was undertaken for the main analysis with an additional analysis from a societal perspective.

The primary health economic outcome was the cost per QALY gained 1 year after randomisation. The primary outcome for the clinical analysis was mortality at 30 days and the economic analysis therefore also used cost per life saved at 30 days and cost per life-year gained at 30 days. Cost analysis was undertaken to present costs at 30 days, costs at ICU discharge, costs at hospital discharge and costs over 1 year from randomisation.

Results

The study set-up and management were challenging. In common with many studies of patients in ICUs, a system to obtain consent/assent in unconscious patients had to be developed and approved in two jurisdictions with differing legal requirements (England and Scotland). As HFOV was a new technique in most study ICUs and was used on some of the highest risk patients, a comprehensive training and support package had to be developed. Recruitment proved difficult, and, as a result, both the study duration and the number of study sites had to be increased.

A total of 795 patients were randomised 1 : 1 to either HFOV or conventional artificial ventilation at 30 study sites. HFOV was used for a median of 3 days (interquartile range 2–5) in 388 patients. The longest initial period of HFOV was 24 days. The primary outcome was 30-day mortality. One hundred and sixty-six of 398 patients (41.7%) in the HFOV group and 163 of 397 patients (41.1%) in the conventional ventilation group died within 30 days of randomisation ($p = 0.85$), for an absolute difference of 0.6% (95% confidence interval -6.1% to 7.5%). The total duration of ICU stay was 16.1 ± 15.2 days in the conventional ventilation group and 17.6 ± 16.6 days in the HFOV group ($p = 0.18$); the total durations of hospital stay were 33.1 ± 44.3 days and 33.9 ± 41.6 days, respectively ($p = 0.79$). The HFOV group received more days of sedative (8.2 ± 6.4 days vs. 9.7 ± 7.4 days; $p = 0.004$) and muscle relaxant (2.0 ± 3.0 days vs. 2.5 ± 3.6 days; $p = 0.044$) medication than the control group. Antibiotic use was similar in both groups (control 12.2 ± 10.3 days, HFOV 13.3 ± 12.5 days; $p = 0.20$).

Data for inpatient resource use were collected on 792 patients (three died before study treatment was started); 397 in the conventional ventilation group and 398 in the HFOV group. Once discharged, 226 patients completed the 6-month questionnaires, 186 patients completed the 12-month questionnaires; 154 carers completed the 6-month questionnaires and at 12 months 108 carers completed the questionnaires. At 1 year following randomisation, the total cost to the NHS including inpatient stay and resources used following discharge was higher in the HFOV group at £44,550 compared with £40,129 in those patients on conventional ventilation to give an incremental cost of £4421. Taking into consideration the cost to the NHS, patient and carers' out-of-pocket expenses and the loss of earnings over 1 year post randomisation, the total cost to society was higher in the HFOV group at £50,583 compared with £45,568 with an incremental cost of £5015.

There was, however, a higher average QALY at 1 year in the HFOV group at 0.302 compared with those patients in the conventional ventilation group at 0.246 with an incremental QALY of 0.056. This gives an incremental cost-effectiveness ratio (ICER) for the cost to society per QALY of £88,790.57 and an ICER for the cost to the NHS per QALY of £78,260. The probability of being cost-effective at a threshold of £20,000 per QALY was 0.18, so the chance of HFOV ever being cost-effective must be considered low.

Conclusions

In conclusion, in a large multicentre effectiveness study, we were unable to find any clinical benefit or harm from the use of HFOV in adult patients with severe type 1 respiratory failure requiring artificial ventilation. A number of uncertainties in the evidence for cost-effectiveness remain but at present there is also no economic justification for the use of HFOV over conventional ventilation in these patients.

We therefore suggest that this mode of ventilation not be used for routine care of patients with severe type 1 respiratory failure requiring artificial ventilation.

However, taking this study's results together with those from the simultaneously reported Canadian OSCILLATE study of HFOV (Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, *et al.* High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;**368**:795–805) which demonstrated an increased mortality in the HFOV group (47% vs. 35% in the control group, number needed to harm = 8), we would also suggest that further research into avoiding ventilator-induced lung injury should concentrate on ventilatory strategies other than HFOV.

Trial registration

This trial is registered as ISRCTN10416500.

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