Conventional ventilatory support versus ECMO for severe adult respiratory failure

Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)

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Executive summary

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Executive summary

Background

Severe respiratory failure has a high mortality in adult patients despite recent advances in intensive care. The fundamental dichotomy of conventional treatment of these patients is that positive pressure ventilation is dangerous when high concentrations of oxygen (fractional inspired oxygen, FiO2) and large tidal volumes/high airway pressures are used, as such ventilation causes ventilator-induced lung injury, which decreases survival. The paradox is that the sickest patients with the severest lung injury require the highest ventilator settings and are most at risk of ventilator-induced lung injury. Extracorporeal membrane oxygenation (ECMO) uses cardiopulmonary bypass technology to support gas exchange in the intensive care unit (ICU) allowing ventilator settings to be reduced, thereby giving the lungs a chance to recover. Although ECMO has been proven in a randomised controlled trial (RCT) to increase survival in severe neonatal respiratory failure, its use in adults has not been similarly validated.

Objectives and entry criteria

CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) was a nationwide UK RCT whose primary hypothesis was that ECMO will improve survival without severe disability at 6 months for adults (18–65 years) with severe (Murray lung injury score ≥ 3.0 or pH < 7.2) but potentially reversible respiratory failure and will be cost-effective.

Funding

The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme and the clinical treatment costs were funded by the NHS via the National Specialist Commissioning Advisory Group for England and Wales and through the Scottish Executive.

Setting

One hundred and three hospitals obtained ethics committee approval to participate, and trial entry was also allowed from centres that did not have ethics committee approval as long as they agreed to transfer the patient to a centre with approval under the Emergency Inclusion Protocol.

Contraindications

Contraindications to trial entry were high pressure/high FiO_2 ventilation (> 30 cm H_2O of peak inspiratory pressure) and/or high FiO_2 (> 0.8) ventilation for more than 7 days; signs of intracranial bleeding; any other contraindication to limited heparinisation; or any contraindication to continuation of active treatment.

Outcome measures

The primary outcome measure was death or severe disability at 6 months. Severe disability was defined as patients being unable to wash or dress themselves and confined to bed. Primary analysis was by intention to treat.

Patients and methods

Between July 2001 and August 2006 enquiries were made about 766 potentially eligible patients from 148 centres. One hundred and eighty of these were randomised from 68 centres, 90 in each arm. Patients were randomised via a telephone call to an automated independent central randomisation service either to continued conventional treatment or to transfer to Glenfield Hospital in Leicester for consideration of ECMO; to ensure close balance between treatment groups for minimisation was used. After the first patient was allocated treatment using simple randomisation, the next patient to enter the trial was allocated to whichever treatment group improved the overall balance according to a pre-selected set of baseline minimisation criteria,

namely type of centre [conventional treatment centre (CTC) or referral hospital (RH)]; age (18–30, 31–45, 46–65 years); hours of high pressure and/or high FiO_2 ventilation (0–48, 49–168); mode of trial entry (i.e. hypoxic/hypercarbic); diagnostic group [pneumonia, obstetric acute respiratory distress syndrome (ARDS), trauma including surgery within previous 24 hours, other ARDS, and other]; and numbers of organs failed (one or two, or three or more) where organ failure was a Sepsis-related Organ Failure Assessment (SOFA) score for that organ of greater than 2. If the patients were randomised to conventional management (CM) and were in a CTC, they remained in the CTC. CTCs were large ICUs that were felt by the local ICU network lead to provide all necessary treatment modalities or, where local ICU networks did not exist, were those units with more than 350 admissions per year that could provide pressure controlled ventilation and haemofiltration. Smaller hospitals that did not fulfil these criteria were classified as RHs. One hundred and forty-eight patients entered the trial from CTCs and 32 from RHs, which included patients entering under the Emergency Inclusion Protocol. If a patient in an RH drew conventional treatment they were transferred by the ECMO transport team to the nearest CTC with a bed available. All patients who drew ECMO were transferred by the same team to Glenfield Hospital for consideration of ECMO. The mean (standard deviation, SD) age at trial entry was 39.9 (13.4) years in the ECMO arm and 40.4 (13.4) years in the CM arm. Primary diagnosis at trial entry was (ECMO/CM) pneumonia 56/53, other ARDS 25/26, trauma or surgery within 24 hours 5/7 and other 4/4. The number of organs failed was (ECMO/CM) one or two in 62/63 patients and more than three in 28/27 patients. Median (interquartile range) duration of ventilation was 35.0 (17.3–104.5) hours in the ECMO arm and 37.0 (15.5–101.5) hours in the CM arm, 28.5 (17.0–69.3) of these hours were at high pressure/high FiO_2 in the ECMO arm and 28.0 (12.0–88.0) in the CM arm. Eighty-five patients entered the ECMO arm for hypoxia (Murray score ≥ 3.0) and 87 entered the conventional arm, the remainder entered because of hypercarbia ($pH < 7.2$). The mean (SD) Murray score was (ECMO/CM) 3.5 (0.6)/3.4 (0.3). The median (IQR) arterial oxygen pressure (PaO_2)/FiO_2 ratio (ECMO/CM) was 73 (57.5–87)/70.5 (60–88) mmHg. All 85 patients in the ECMO arm who entered because of hypoxia fulfilled the American–European consensus definition of ARDS. In the conventional arm, 87 patients entered based on hypoxia, 84 fulfilled the ARDS criteria and two the acute lung injury criteria.

Results

Of the 90 patients randomised to the ECMO arm, 68 received that treatment. ECMO was not given to three patients who died prior to transfer, two who died in transit, 16 who improved with conventional treatment given by the ECMO team and one who required amputation and could not therefore be heparinised. Ninety patients entered the CM (control) arm, three patients later withdrew and refused follow-up (meaning that they were alive), leaving 87 patients for whom primary outcome measures were available. CM consisted of any treatment deemed appropriate by the patient's intensivist with the exception of extracorporeal gas exchange. The low volume ventilation strategy from the ARDS Network (ARDSNet) study was recommended. No CM patients received ECMO, although one received a form of experimental extracorporeal arteriovenous carbon dioxide removal support (a clear protocol violation). Fewer patients in the ECMO arm than in the CM arm had died or were severely disabled 6 months after randomisation, [33/90 (36.7%) versus 46/87 (52.9%) respectively; relative risk (RR) = 0.69 [95% confidence interval (CI) 0.50 to 0.97]; $p = 0.030$]. This equated to one extra survivor for every six patients treated. Only one patient (in the CM arm) was known to be severely disabled at 6 months.

Economic evaluation

Previous studies of ECMO had not estimated the additional costs or the consequences of treatment. However, the high costs of intensive care and changes in resource use and quality of life resulting from changes in clinical outcome suggested the potential for ECMO treatment to have an important economic impact in the NHS. Full economic evaluation was therefore built into the CESAR trial. The economic data collection and economic analysis took the perspectives of the NHS and of the household.

Data about resource use and economic outcomes [quality-adjusted life-years (QALYs)], were collected from participating patients. Estimated QALYs were based on EuroQol 5 dimensions (EQ-5D) responses at 6 months and were weighted using UK population values for health states. Studies of the key cost-generating events were undertaken, and analyses of cost–utility at 6 months post randomisation and modelled lifetime cost–utility were performed.

Lifetime QALYs were estimated based on the assumption that the quality of life of all surviving patients improved up to 24 months from randomisation, and that at 24 months their health states were the same as those of other adults of similar age and gender in the UK population. It was also assumed that all survivors had the same average life expectancy as adults of similar age and gender in the UK population. This assumption was based on our experience of long-term follow-up of patients who had been previously treated with ECMO.

Patients allocated to ECMO incurred average total costs of £73,979 compared with £33,435 for those undergoing CM (UK prices, 2005). At 6 months post randomisation, the additional cost of a survivor without severe disability of ECMO compared with CM was £251,360. ECMO treatment resulted in 0.03 predicted additional QALYs at 6 months' follow-up. A lifetime model predicted the cost per QALY of ECMO to be £19,252 (95% CI £7622 to £59,200) at a discount rate of 3.5%. Lifetime QALYs gained were 10.75 for the ECMO group compared with 7.31 for the conventional group.

Costs to patients and their relatives, including out of pocket and time costs, were higher for patients allocated to ECMO.

Conclusions

A major limitation of this study is the lack of standardisation of care in the conventional arm. This was because it was not possible for the conventional intensive care providers to reach a consensus as to what constituted optimal care. An alternative strategy of transferring all the patients to Glenfield to be cared for by the ECMO team was dismissed by collaborators as they did not consider the ECMO team to be sufficiently expert in the provision of conventional intensive care. The other possibility considered was to use a single centre to provide all of the conventional care, but this was impossible as such a centre does not exist in the UK. The trial team therefore took the pragmatic decision to recommend what was proven to be the best ventilation strategy (the low volume ARDSNet protocol) but allow individual intensivists to determine what they thought was the best treatment for their patients. If this decision had not been taken then it would not have been possible to conduct the study. This pragmatic design meant that CESAR was comparing treatment in an expert centre where ECMO was part of the treatment algorithm with the treatment available to the general public in the UK as a whole. Compared with CM, transferring adult patients with severe but potentially reversible respiratory failure to a single centre specialising in the treatment of severe respiratory failure for consideration of ECMO significantly increased survival without severe disability. Use of ECMO in this way is likely to be cost-effective when compared with other technologies currently competing for health resources.

Trial registration

This trial is registered as ISRCTN47279827.

Publication

Peek GJ, Elbourne D, Mugford M, Tiruvoipati R, Wilson A, Allen E, *et al.* Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess* 2010;**14**(35).

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

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Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 99/01/01. The contractual start date was in July 2000. The draft report began editorial review in May 2008 and was accepted for publication in June 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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