CRITICAL CARE

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Ave, CESAR, morituri te salutant! (Hail, CESAR, those who are about to die salute you!)

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Expanded abstract

Citation

Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009, 374:1351-1363. [1].

Background

Severe acute respiratory failure in adults causes high mortality despite improvements in ventilation techniques and other treatments (e.g., steroids, prone positioning, bronchoscopy, and inhaled nitric oxide).

Methods

Objective: We aimed to delineate the safety, clinical efficacy, and cost-effectiveness of extracorporeal membrane oxygenation (ECMO) compared with conventional ventilation support.
Design: Randomized controlled trial.
Setting: UK-based multicenter trial from July 2001 to August 2006.
Subjects: 180 adults aged 18–65 years with severe (Murray score >3.0 or pH <7.20) but potentially reversible respiratory failure. Exclusion criteria were: high pressure (>30 cm H_2O of peak inspiratory pressure) or high FiO_2 (>0.8) ventilation for more than 7 days; intracranial bleeding; any other contraindication to limited heparinization; or any contraindication to continuation of active treatment.
Intervention: Subjects were randomly assigned in a 1:1 ratio to receive continued conventional management or referral to consideration for treatment by ECMO.
Outcomes: The primary outcome was death or severe disability at 6 months after randomization or before discharge from hospital. Primary analysis was by intention to treat. Only researchers who did the 6-month follow-up were masked to treatment assignment. Data about resource use and economic outcomes (quality-adjusted life-years) were collected. Studies of the key cost generating events were undertaken, and we did analyses of cost-utility at 6 months after randomization and modeled lifetime cost-utility.

Results

766 patients were screened; 180 were enrolled and randomly allocated to consideration for treatment by ECMO (n=90 patients) or to receive conventional management (n=90). 68 (75%) patients actually received ECMO; 63% (57/90) of patients allocated to consideration for treatment by ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (relative risk 0.69; 95% CI 0.05-0.97, p=0.03). Referral to consideration for treatment by ECMO led to a gain of 0.03 quality-adjusted life-years (QALYs) at 6-month follow-up. A lifetime model predicted the cost per QALY of ECMO to be £19 252 (95% CI 7622-59 200) at a discount rate of 3.5%.

Conclusions

We recommend transferring of adult patients with severe but potentially reversible respiratory failure, whose Murray score exceeds 3.0 or who have a pH of less than 7.20 on optimum conventional management, to a centre with an ECMO-based management protocol to significantly improve survival without severe disability. This strategy is also likely to be cost-effective in settings with similar services to those in the UK. (ISRCTN47279827)

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Commentary

The use of ECMO for the treatment of acute respiratory failure in adults has been debated since the mid-1970s. Prior to the publication of the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial results, there were two negative randomized controlled trials [2,3] in contradistinction to a number of positive institutional experiences [4-7]. The relevancy of these randomized trials to modern ECMO has been questioned due to issues of case selection, ventilation strategies, extracorporeal circuit design, and disease management that were completely different from modern protocols.

CESAR is the first contemporary randomized controlled trial of ECMO referral for respiratory failure in adults compared to conventional supportive critical care. Importantly, the intervention in CESAR was *referral* to an ECMO center not *treatment* with ECMO. In fact, only 75% of ECMO-referred patients actually received ECMO. Despite this limited application, the two major effects of the intervention were impressive. First, management of adults with severe respiratory failure at a center that has ECMO capability resulted in increased 6-month survival without severe disability compared to conventional management. Second, referral to a center that has ECMO capability was cost-effective from the perspective of the UK National Health Service. The absolute risk reduction for the primary outcome was 16%, which translates into a number-needed-to-treat of 6.2 patients. Put another way, the intervention will result in one additional life saved for every 6.2 in whom it is attempted, compared to conventional management.

Strengths of the trial were an early assignment to treatment groups, intention-to-treat analysis, incorporation of transport risk into trial design, and a robust economic analysis. The forethought of their design allows the findings to be considered pragmatically and reconciles some unanswered questions regarding ECMO use. Importantly, the study shows that ECMO *referral* is beneficial – rather than the narrower question of only ECMO use. This distinction allows a broader take on the study findings. The overwhelming majority of hospitals responsible for the management of adults with severe respiratory failure do not have ECMO capabilities, though they are responsible for the decision to refer patients to a center that does.

Despite the strengths of this study, there are several limitations that challenge both the generalizability and validity of the findings. As the management of patients randomized to ECMO-consideration was performed at an expert high case volume center, it bears questioning whether the results would be similar in smaller or less experienced centers [8]. Furthermore, the argument can be made that the findings are specific to the United Kingdom's health care system and not generalizable to other health care networks. In fact, the translation of currency into US dollars should really only be interpreted for scale, rather than as a reflection of cost-effectiveness from a US perspective. Three patients in the conventional group who were known to be alive at 6 months but who asked to be withdrawn from the study were excluded from the calculation of the primary endpoint due to missing information about severe disability. As the authors point out, assuming that these three patients had all been severely disabled, or had not been severely disabled, the relative risk of the primary outcome would be 0.67 (95% CI 0.48–0.94, p=0.017), and 0.72 (0.51–1.01, p=0.051), respectively. In the latter comparison, the primary endpoint narrowly misses the threshold for significance.

A more concerning aspect of the study was the lack of a management protocol for patients randomized to conventional treatment, leaving the reader to wonder if the ECMO referral group was compared to an appropriate standard of care. The authors indicate there was a difference of 23% between treatment groups with respect to the use of a lung protective ventilation strategy at any time. Could lower adherence to this strategy in the conventional management group account for the mortality difference observed or was it universally attempted but not possible in the sickest patients due to the severity of their underlying disease? We wonder.

The CESAR trial clearly informs our understanding of the role of ECMO referral in a modern health care network, but will likely not represent the final referendum on this technology. Further study is needed to show that the results of CESAR are not merely specific to the single ECMO center in the study or to the United Kingdom, but that they apply to all adults with severe respiratory failure. The cost-effectiveness analysis is encouraging, but modeling in other health care environments would be needed prior to wholesale adoption. Ultimately, ECMO will likely remain a luxury commodity without high-volume use, and as such will continue to have a place in the management of severe respiratory failure at referral centers – independent of cost-effectiveness. Will new challenges such as influenza H1N1 force us to reconsider the economic burden of ECMO [9]? If so, the optimal positioning of centers with this capability will need to be determined as will protocols for initiating referrals and transfers. Time and circumstance will tell.

Recommendation

Referral of adult patients with severe respiratory failure to an ECMO-capable facility results in improved 6-month survival without disability and is cost-effective from the standpoint of the UK National Health Service. Replication of the CESAR findings will establish whether

the trial describes a limited institutional experience or offers a preferred management strategy for patients with severe respiratory failure.

Competing interests
The authors declare that they have no competing interests

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