Enferm Intensiva. 2020;31(1):41–43

Enfermería Intensiva

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COMMENTS TO RESEARCH ARTICLES

ECMO: Commentary of the EOLIA trial on the use of Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome☆

ECMO: Comentario del ensayo EOLIA sobre el uso de la membrana de oxigenación extracorpórea en el síndrome de distrés respiratorio agudo

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. Combes A., Hajage D., Capellier G., Demoule A., Lavoué S., Guervilly C., et al. N Engl J Med. 2018;378(21):1965-75, doi:10.1056/NEJMoa1800385.

Abstract

Background The efficacy of venovenous extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome (ARDS) remains controversial.

Methods In an international clinical trial, we randomly assigned patients with very severe ARDS, as indicated by one of three criteria—a ratio of partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 50 mm Hg for more than 3 h; a Pao2:Fio2 of less than 80 mm Hg for more than 6 h; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for more than 6 h—to receive immediate venovenous ECMO (ECMO group) or continued conventional treatment (control group). Crossover to ECMO was possible for patients in the control group who had refractory hypoxemia. The primary end point was mortality at 60 days.

Results At 60 days, 44 of 124 patients (35%) in the ECMO group and 57 of 125 (46%) in the control group had died (relative risk, 0.76; 95% confidence interval [CI], 0.55–1.04; P = 0.09). Crossover to ECMO occurred a mean (±SD) of 6.5 ± 9.7 days after randomization in 35 patients (28%) in the control group, with 20 of these patients (57%) dying. The frequency of complications did not differ significantly between groups, except that there were more bleeding events leading to transfusion in the ECMO group than in the control group (in 46% vs. 28% of patients; absolute risk difference, 18 percentage points; 95% CI, 6–30) as well as more cases of severe thrombocytopenia (in 27% vs. 16%; absolute risk difference, 11 percentage points; 95% CI, 0–21) and fewer cases of ischemic stroke (in no patients vs. 5%; absolute risk difference, −5 percentage points; 95% CI, −10 to −2).

Conclusions Among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy. (Funded by the Direction de la Recherche Clinique et du Développement and the French Ministry of Health; EOLIA ClinicalTrials.gov number, NCT01470703. opens in new tab).

Commentary of the trial

Extracorporeal membrane oxygenation systems (ECMO) are principally used in three indications: to maintain abdominal organs in donors; as cardiocirculatory support and as rescue therapy in respiratory support. Despite appropriate mechanical ventilation and the other care offered in intensive care units, severe acute respiratory distress syndrome (ARDS) may lead to hypoxia and therefore death. The mechanisms with which this technique may reduce mortality are mainly that of correcting lethal hypoxia and enabling protective ventilation which reduces the damage associated

DOI of original article: https://doi.org/10.1016/j.enfi.2020.01.002

☆ Please cite this article as: Naharro-Abellán A, Abella-Álvarez A. ECMO: Comentario del ensayo EOLIA sobre el uso de la membrana de oxigenación extracorpórea en el síndrome de distrés respiratorio agudo. Enferm Intensiva. 2020;31:41–43.

Extracorporeal Membrane Oxygenation for Severe Acute Respira-tory Distress Syndrome. Combes A., Hajage D., Capellier G., Demoule A., Lavoué S., Guervilly C., et al. N Engl J Med. 2018;378(21):1965-75, doi: 10.1056/NEJMoa1800385.

with mechanical ventilation. However, no technique is free from complications and despite the improvement of gaseous exchange, haemorrhaging, infections and embolisms, among other complications, may arise.

Since its introduction into clinical practice complications have dropped whilst ARDS management has improved and with it, prognosis. The use of ECMO increased as a result of the CESAR[1] study, where a protocol which included referring patients to centres where ECMO was used, decreased mortality, together with the publication of retrospective data during the pandemic of A influenza serotype H1N1. Despite these favourable results, scientific evidence is still disputed: studies without a group control, not all the patients of the ''ECMO'' group received this therapy in the CESAR trial, and there were different inclusion criteria and different management protocols.

The main aim of the EOLIA trial was to assess whether the early use of ECMO reduced mortality in severe SDRA compared with the control group. The patients of the ''ECMO'' group were percutaneous cannulated after randomisation. Within the control group the use of ECMO was permitted if the patient maintained a SatO2 < 80% for 6 h, after initiation of all additional available measures, and if the attending physician believed that multi-organ failure was not irreversible and ECMO could alter the result. General management in both groups was protocolised and followed the regular recommendations of ARDS which included the use of protective mechanical ventilation, the prone position and neuromuscular relaxation. The study was terminated due to futility with 249 randomised patients. The mortality observed was 11% less in the ECMO group (35% vs. 46%), without statistical significance being reached.

Critical commentary

It should be emphasized that this study did not truly analyse the isolated benefit of the ECMO, since its use was permitted as rescue therapy in the control group. It may be stated that it analyses two management protocols where ECMO may be used. Twenty eight per cent of the control group received ECMO as rescue therapy. This subgroup of patients at randomisation were less compliant, had greater distending pressure and greater extension of infiltrates. Their mortality was higher than that of the patients in the control group who did not receive ECMO (57% vs. 41%) and that of the patients of the ECMO group (57% vs. 35%). Although it would have been interesting because it could have indicated which patients ECMO should be used earlier, in the trial the mortality of the subgroup of control patients who finally received ECMO was not compared with that of the patients of the ECMO group with similar severity.

The trial was prematurely cut short, reducing its potential. Ethically it is justifiable to terminate a trial which is not believed to be positive, due to exposing patients to an unnecessary intervention, but this decision has been up for debate, as being at the limit of statistical significance and the existence of possible confusing aspects, such as the before-mentioned cross-over.

In order to assess the isolated effect of ECMO on survival, two sub-analyses were presented: (1) Death of patients in the ECMO group and death of control patients or those who passed onto ECMO. The event occurred in 58% of the control group compared with 35% of the ECMO group with a relative risk (RR) of .62 (95% CI: .47–.82). These results are difficult to interpret whilst bearing in mind that the pre-established criteria for rescue with ECMO had a subjective component. (2) ''rank-preserving structural-failure time model (RPSFM)''. This assumes that treatment increases survival depending on the time which this treatment is applied and survival of the control group is recalculated as if the treatment had never been administered. This analysis obtains a hazard ratio for mortality at 60 days of .51 as a result, which was not statistically significant (95% CI: .24–1.02). Furthermore, as it was not significant, this model did not take into account that the benefit could vary depending on the treatment applied.

Given that recruitment speed was low, 249 patients in 6 years, it is improbable that such a complex trial will be conducted in the near future to re-assess the use of ECMO in ARDS. It is therefore important to extract as much information as possible from the data available, and for this reason Goligher et al. have published a post-hoc Bayesian analysis of the trial.[2]

Bayesian analysis

The EOLIA trial concluded that the ECMO did not reduce mortality. In contrast to this, using the same data, Goligher et al.[2] were able to show that the ECMO reduced mortality. How is it possible that the same data with the two analyses had different results? If this trial did contribute information, in what situation should we use ECMO?

To understand the Bayesian analysis first an initial reminder of the frequentist approach is needed. This includes the most standard analysis, such as Chi-squared or the Student's t-test, focusing on assessing whether the differences between the two groups (intervention and control) may be due to chance. Normally they conclude that if probability (p) is lower than .05, chance does not justify the differences and the intervention affects the result.[3]

Bayesian analysis combines previous information, which may be a combination of subjective opinions and meta-analysis of previous trials, with new data. It calculates a probability, directly, that a conclusion is true. Unlike frequentist analysis its gives a probability as a result, not only positive or negative results.

Using the tools described, different probabilities are calculated: that the ECMO will lead to an improvement in survival (RR < 1), that the absolute risk reduction (ARR) will be below 2%, that there would be at least 4% and thus successively up to 20%, the value stated in the EOLIA trial.

To minimize the subjective aspect and improve the consistency of analysis several calculations were made with subjective opinions, which ranged from enthusiastic to sceptical and the weight of previous trials varied in several percentages, reflecting different estimations in their relevance. If the conclusions do not depend on previous information, or changes are minimal, results are consistent.

According to this analysis early ECMO reduces mortality, with a RR < 1, regardless of previous data, with a probability between 88–99% (depending on the previous information) that it was true. However, the probability of reducing

mortality by 20% or more falls between 0 and 48% depending on the preliminary data.

Integrating both analyses

In reconsideration of the previously proposed questions ''how is it possible that the same data with two analyses offer different results? The Bayesian analysis adds to the original statistical study, that the ECMO improves survival to a certain level, but without clarifying whether the benefit it confers is relevant. It does not contradict, but instead supports the conclusion that there is not such a large benefit as that of a 20% of ARR.

What situation should be use ECMO in? The recommendation that may be concluded after assessing both analyses are similar to those already existing in the literature.[4] What the Bayesian analysis offers is a mathematical model which includes the results of a study with previous information. This process is carried out with another methodology, in creation of several recommendations.

The veno-venous ECMO should be considered in patients with refractory respiratory failure instead of other measures. It should form part of an overall management which includes the use of protective mechanical ventilation and at least a change to the prone position. Measures such as the prone position improve survival and improve prognosis if ECMO is rendered necessary.[5]

Conclusions

In view of the difficulty in conducting this type of trial and the complexity of critically ill patients, other sources of information must be used, such as new statistical techniques (Bayesian analysis) to take advantage of all the information offered by each trial. In managing ARDS it is important to optimise mechanical ventilation and the use of the prone position. Veno-venous ECMO is a rescue measure, the precise best moment of usage of which is currently unknown.

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