AAST Critical Care Committee
Journal Review

Name of Reviewer

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Title of Article

- Dexamethasone Treatment for the Acute Respiratory Distress Syndrome: A Multicentre, Randomised Controlled Trial

Article Reference

- Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respiratory Medicine. 2020;8(3):267-276.

Link to Article

- https://pubmed.ncbi.nlm.nih.gov/32043986/

Context

No proven pharmacologic intervention exists for the treatment of patients suffering from acute respiratory distress syndrome (ARDS). However, corticosteroids have been investigated in multiple prior studies and trials to mitigate the inflammatory surge which occurs in the lungs.[1] The Society of Critical Care Medicine and the European Society of Intensive Care Medicine performed a meta-analysis in 2017, comprised of nine, small randomized clinical trials, to evaluate the role of prolonged corticosteroid (methylprednisolone or hydrocortisone) administration in early and late moderate and severe ARDS.[2] The analysis found that the use of corticosteroids in early moderate to severe ARDS (i.e. within 14 days of onset) resulted in a significant decrease in systemic inflammatory markers (cytokines and/or C-reactive protein levels) and ventilator days. A mortality benefit remains in question. Dexamethasone has been shown to be more potently anti-inflammatory than other corticosteroids and to have fewer mineralocorticoid properties, resulting in less edema.[3,4] No published randomized controlled trials existed in the literature, prior to this investigation, to evaluate the role of dexamethasone in the treatment of ARDS.

Methods

A multicenter, open-label, randomized controlled trial was performed in 17 intensive care units across medical teaching institutions in Spain, prior to the SARS-COv-2 pandemic. Patients meeting inclusion criteria were 18 or older, mechanically ventilated with a new diagnosis of moderate to severe ARDS, as defined by the European Consensus Criteria for ARDS or Berlin Criteria.[5,6] A strategy involving a run-in period (termed “enrichment period”) in which patients were subsequently randomized was defined as a PaO2/FiO2 ratio less than 200 for at least 24 hours with standardized ventilator settings. Patients were excluded if pregnant or actively lactating, brain dead, DNR status, diagnosed with terminal-stage cancer or other disease, treated with corticosteroids or immunosuppressant drugs, enrolled in another experimental trial, and/or diagnosed with congestive heart failure or chronic obstructive pulmonary disease. Patients meeting inclusion criteria were randomly assigned to conventional treatment or conventional treatment plus intravenous dexamethasone. Patients in the dexamethasone group received a dose of 20 mg intravenous dexamethasone on treatment days 1-5 followed by 10 mg of dexamethasone on days 6-10. Physicians were not blinded to the administration

of dexamethasone and the conventional treatment arm did not include placebo. If extubation occurred before treatment day 10, dexamethasone was discontinued. Conventional treatment was defined as a tidal volume of 4-8 ml/kg predicted bodyweight, a plateau pressure < 30 cm H2O, a respiratory rate to maintain PaCo2 between 35-50 mm Hg, and PEEP/FiO2 combinations per the ARDSNet protocol.[7]

Findings

A total of 1,006 patients were assessed for eligibility between March 28, 2013 and December 31, 2018. Ultimately, 277 met inclusion criteria and were randomly assigned with 139 receiving dexamethasone and the remainder serving as control. The trial was stopped by the data and safety monitoring board secondary to low enrollment rate; at the time of cessation, the trial had enrolled more than 88% (277/314) of the planned sample size. There were no differences between groups in terms of baseline characteristics, number of patients receiving continuous neuromuscular blocker infusion nor the use of recruitment maneuvers. The median number of treatment days was 10. No patients were readmitted to the ICU within 60 days in either group. The cause of ARDS was pneumonia in 147 patients (53%) and sepsis in 67 patients (24%).

Major findings (treatment versus control):

- Ventilator-free days at 28: 12.3 (SD 9.9) versus 7.5 (SD 9.0), p < 0.0001 (**primary outcome**)
- All-cause mortality at day 60: 29 (21%) versus 50 (36%), p = 0.0047 (**secondary outcome**)
- ICU mortality: 26 (19%) versus 43 (31%), p = 0.0166
- Hospital mortality: 33 (24%) versus 50 (36%), p = 0.0235

Complications (treatment versus control):

- Hyperglycemia in ICU: 105 (76%) versus 97 (70%), p = 0.33
- New infections in ICU: 33 (24%) versus 35 (25%), p = 0.75
- Barotrauma: 14 (10%) versus 10 (7%), p = 0.41

Commentary

This randomized, controlled, multi-center trial is the first to date evaluating the efficacy of intravenous dexamethasone for the treatment of moderate to severe ARDS in adult patients receiving lung-protective ventilation. The primary outcome is a significant benefit of the intervention in terms of ventilator-free days versus usual care. This trial is inclusive of multiple ARDS etiologies and the enrichment strategy allows for screening of patients at highest risk of death prior to randomization, contributing to its generalizability. Importantly, the authors assert that 1 death in each 60-day period was avoided for every 7 patients treated with dexamethasone. No increased incidence in adverse effects was observed in the treatment group, inclusive of hyperglycemia, infections, and barotrauma.

Limitations

External Validity

Adult subjects were included in the study who were diagnosed with moderate to severe ARDS. Patients were excluded from the study if the treating physician identified corticosteroid-sensitive pathologies which would be expected to benefit from steroid administration (250 of 630 excluded patients). Unfortunately, these corticosteroid-sensitive conditions were not further delineated by the authors in the manuscript. In the appendix, the authors mention a large number of patients were excluded from the study as ER and ICU physicians administered steroids for sepsis and pneumonia prior to the development of ARDS. Additionally, patients with common comorbidities were excluded from the study such as congestive heart failure, immunocompromise and chronic obstructive pulmonary disease. As many of our critically ill patients suffer from these conditions, this limits the generalizability of the findings of the study.

Seventy-seven percent of patients undergoing trial randomization were diagnosed with pneumonia or septic shock. It is difficult to assess whether dexamethasone administration would benefit patients with ARDS of other etiologies such as pancreatitis, trauma, meningitis, burn inhalation, and transfusion-related lung injury. The study included both medical and surgical patients. Complications commonly associated with steroid use such as wound infection and delayed or poor wound healing were not assessed. The infections tracked by the investigators included pneumonia, sepsis, UTI, empyema, and tracheobronchitis only.

Finally, 14 patients were included in the study who were treated with extracorporeal lung support (5 in the treatment group and 9 in the control group). The authors note mortality was assessed without the inclusion of these patients and assessed if all of these patients were counted as deaths. Both of these statistical scenarios altered the rate of mortality published by the authors but still revealed statistically significant improvement in survival. However, the study may have been strengthened by the exclusion of these patients altogether. Taken together, the external validity of the study is limited by the inclusion and exclusion of these groups of patients.

Methodology

The investigators found that more patients in the dexamethasone group required re-intubation in the 28-day period after randomization compared to the control group, though their actual duration of mechanical ventilation was statistically shorter. This may be influenced by two factors: 1) lack of blinding and 2) the absence of standardized extubation practices. The increased rate of re-intubation in the dexamethasone group may indicate these patients were more aggressively weaned from the ventilator which would, in turn, affect the primary outcome measure of ventilator-free days.

Dexamethasone dosing optimization was not evaluated. Future studies will be needed to investigate this issue as a protocol which reaches maximum steroid benefit while minimizing the negative effects of steroid administration is desirable. Of note, the authors found no difference in ICU mortality between patients receiving dexamethasone for 1 week or less versus those receiving dexamethasone up to 10 days after randomization.

Finally, the trial was discontinued early by the data and safety monitoring board due to low recruitment; an 88.2% goal enrollment was achieved. Enrollment sharply declined in 2017. In the appendix, the authors note 6 possible explanations for decreased enrollment:

- five centers ceased study participation secondary to “reasons unrelated to the trial”
- a national prevention program in Spain was instituted for treating sepsis
- ICU physicians became increasingly aware of preventing ventilator-associated pneumonia
- patients were increasingly excluded for having received steroids for sepsis or pneumonia in the ER or early in an ICU stay
- reduction in prevalence of moderate to severe ARDS

The power of the study would clearly have been improved had more patients been enrolled. However, the treatment effect was significant and greater than expected. In the population of ARDS patients analyzed, early administration of dexamethasone likely does improve mortality and ventilation duration.

Implications

This trial provides level I evidence that the early administration of dexamethasone improves mortality and ventilation duration in patients with moderate to severe ARDS receiving lung-protective ventilation. This evidence is supported by prior recommendations from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, although other corticosteroid agents were previously employed. As

dexamethasone provides significant anti-inflammatory benefit and little mineralocorticoid function, it may prove to be the optimal corticosteroid for the treatment of ARDS. Further research is needed to verify these findings in different populations and amongst patients with confounding comorbidities and to ensure the most efficacious dosing regimen.

References

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