Best Evidence in Critical Care Medicine

Steroids in fibroproliferative acute respiratory distress syndrome: approach with care

Article appraised

Steinberg KP, Hudson LD, Goodman RB, et al.; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006; 354: 1671–84.

Structured abstract

Question: Do steroids improve survival in patients with patients with persistent acute respiratory distress syndrome?

Design: Multicentre, randomized, double-blind placebo-controlled trial.

Setting: Twenty-five US member hospitals of the National Heart, Lung, and Blood Institute (NHLBI) Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network.

Patients: One hundred eighty patients who were intubated and receiving mechanical ventilation for ARDS, enrolled between seven and 28 days after disease onset, and recruited over a six-year period. Exclusion criteria included conditions that were major relative contraindications to the immunosuppressive effect of steroids, and conditions that were otherwise strong relative indications for steroids. The former were primarily ongoing sepsis, while the latter included vasculitis, diffuse alveolar hemorrhage, and pre-existing steroid dependency. Of 4,123 patients screened, 66% were excluded for explicitly documented pre-determined reasons. A further 28.8% (946 patients) were excluded for "other" reasons. Baseline characteristics were similar between groups, although there were more females in the treatment group.

Intervention: Patients were randomly assigned (using permuted blocks) to placebo or intravenous methylprednisolone as follows: bolus 2 $mg \cdot kg^{-1}$ of predicted body weight, followed by 0.5 $mg \cdot kg^{-1}$ every six hours for 14 days, then 0.5 $mg \cdot kg^{-1}$ every 12 hr for seven days. The study drug was tapered over two to four days. The study included a ventilation protocol that required daily weaning assessments.

Main outcomes: The primary outcome was mortality at 60 days after enrolment; secondary outcomes included the number of ventilator-free and organ failure-free days in the first 28 days, the incidence of infectious complications during the first 28 days, and the changes in markers of inflammation and fibroproliferation on study day seven.

Main results: There was no significant difference in 60-day mortality, with 26 deaths (29.0%) in each group; this equivalence persisted at 180 days (31.9% placebo mortality, 31.5% study mortality). Study patients were able to breathe without assistance slightly sooner than placebo patients, but required more frequent resumption of ventilation. Study patients also had significantly fewer days in the intensive care unit (ICU) during the first 28 days, but not at day 180. Significant improvements in PaO_2:F_IO_2 ratios, plateau pressures, and respiratory compliance were noted during the study period. However, despite these minor physiologic alterations, no significant differences were seen between groups in the median number of ICU days, nor the ultimate duration of hospitalization. Of note, treatment with methylprednisolone was associated with a significantly increased mortality among patients who had had ARDS for more than 13 days before enrolment. In addition, serious adverse reports of neuromyopathy were noted in nine patients, all of whom were in the methylprednisolone group.

Conclusion: In this clinical trial of 180 patients with persistent ARDS, there was no effect of corticosteroids on survival. Moreover, steroids appeared to increase the severity of concomitant neuromyopathy, and seemed harmful to patients enrolled at least 14 days after the onset of ARDS. These results do not support routine use of methylprednisolone in patients with persistent ARDS.

Commentary

Acute respiratory distress syndrome (ARDS) is a devastating condition for which there are few effective therapies. Despite the historical suggestion of benefit from steroids based on a small case series reported by Meduri *et al.*,[1] this clinical trial provides the most

convincing evidence to date that corticosteroids do not improve outcomes in severe and persistent ARDS. Although improvement in a number of minor physiologic parameters was demonstrated, survival at 60 and 180 days was not altered. Furthermore, the duration of hospitalization did not differ significantly between groups. In addition, methylprednisolone appeared to increase the risk of severe critical illness neuromyopathy. As well, the duration of ARDS before treatment appeared to interact significantly with the effect of corticosteroids on survival: patients enrolled at least 14 days after disease onset who received methylprednisolone had a significantly higher case fatality rate. Despite a small imbalance in lung injury scores, in this subgroup, corticosteroids appeared to cause actual *harm*.

Some study limitations were noteworthy. Only 5% of eligible patients were enrolled over a six-year period, with 8% (250 patients) declined by the patient's primary physician, and a further 29% (946 patients) excluded for unspecified reasons, limiting the generalizability of the results. Further, the study was not published until 30 months after the completion of data collection. Significantly more females were present in the treatment group, and the influence of gender on steroid metabolism may affect outcome. Average blood glucose levels were marginally higher in the study group at several points during the trial, which may have contributed to neuromyopathy. Finally, the proportion of patients with suspected or probable pneumonia was lower in the study group than in the placebo group.

Although this trial may be criticized on a number of points, it does not support the routine use of steroids in patients with established ARDS. There likely exists a specific subset of patients that would be harmed by the addition of corticosteroids, and this trial provides some insight into this group. Unfortunately, as our understanding of the inhomogeneous disease of ARDS remains limited, so do the therapies available. In spite of this, the possible application of steroids in select populations remains enticing. Meduri has suggested several possible effective mechanisms: glucocorticoid treatment has been associated with significant reductions in laboratory markers of systemic inflammation.[2] The notion of endogenous glucocorticoid insufficiency in the control of inflammation, and resulting inflammation-induced peripheral glucocorticoid resistance in ARDS, are also possible contributory mechanisms.[3] Finally, Meduri has also demonstrated that the molecular downregulation of a pro-inflammatory receptor (nuclear factor κB) by glucocorticoids is important for the resolution of systemic and pulmonary inflammation in ARDS.[4] Unfortunately, the pathophysiology of ARDS remains more complex than this, as is demonstrated by the equivalent outcomes in the treatment and placebo groups of this study. Until we are better able to stratify patients with ARDS, and determine the presence of dysregulated inflammation and glucocorticoid resistance, steroids in ARDS should be considered with caution.

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