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Journal club critique

Hydrocortisone infusion may improve survival in patients with severe community-acquired pneumonia

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Expanded Abstract

Citation

Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della PR, Giorgio C, Blasi F, Umberger R, Meduri GU: Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005, 171:242-248 [1].

Hypothesis

Hydrocortisone infusion in severe community-acquired pneumonia (CAP) attenuates systemic inflammation and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications.

Methods

Design: Prospective, randomized, double-blind, placebo-controlled multi-center clinical trial.

Setting: Intensive care units and respiratory intermediate units of six hospitals in Italy between July 2000 and March 2003.

Subjects: Forty-six patients admitted to the intensive care unit with clinical and radiographic evidence of pneumonia and either two minor or one major 1993 American Thoracic Society criterion for severe pneumonia. Patients with nosocomial pneumonia, immunosuppression, acute burn injury, pregnancy, life expectancy less than 3 months, and conditions requiring more than 0.5 mg/kg/day of prednisone equivalent (such as acute asthma and COPD) were excluded.

Intervention: Subjects were randomly assigned to receive hydrocortisone infusion or placebo in addition to protocol guided antimicrobial therapy. Hydrocortisone was given as an intravenous 200mg bolus followed by infusion at a rate of 10 mg/hour for 7 days.

Outcomes: The primary end-points of the study were improvement in PaO_2:FiO_2 (PaO_2:FiO_2 >300 or ≥100 increase from study entry) and multiple organ dysfunction syndrome (MODS) score by Study Day 8, and development of delayed septic shock. The secondary end-points were duration of mechanical ventilation, length of ICU and hospital stay, and survival to hospital discharge and to 60 days.

Results

The hydrocortisone group had lower PaO_2:FiO_2, higher chest radiograph score and C-reactive protein (CRP) level at study entry. However by study day 8, treated patients had, compared with control subjects, a significant improvement in PaO_2:FiO_2 ($p=0.002$) and chest radiograph score ($p<0.0001$), and a significant reduction in CRP levels ($p=0.01$), MODS score ($p=0.003$), and delayed septic shock ($p=0.001$). Hydrocortisone treatment was associated with a significant reduction in length of hospital stay ($p=0.03$) and mortality ($p=0.009$). There were seven deaths in the control group, whereas none in the hydrocortisone group.

Conclusion

A seven-day course of low-dose hydrocortisone infusion in patients with severe community-acquired pneumonia was associated with a significant reduction in duration of mechanical ventilation, hospital length of stay, and hospital mortality.

Commentary

The role of glucocorticoids in patients with severe CAP is uncertain. In patients with septic shock, however, several recent randomized controlled trials have shown that low doses of glucocorticoids administered for a prolonged period of time shorten the duration of shock and improve survival [2-4]. Although some of the patients in these studies

had CAP as a source of sepsis, patients with CAP were not analyzed separately. The study by Confalonieri and colleagues is the first randomized study to evaluate the efficacy and safety of low-dose hydrocortisone infusion specifically in patients with severe CAP. The investigators in this trial also attempted to explore the role of corticosteroids in attenuating inflammatory response as assessed by serum CRP levels. Previous studies assessing the role of glucocorticoids in patients with CAP found no benefit in terms of inflammatory mediator release but these studies either used shorter courses of glucocorticoids or were not powered to detect treatment differences [5-7].

The authors in the current study used a sequential trial design with interim analyses approximately every 20 patients in order to reduce the number of patients exposed to "inferior" treatment through early study termination if treatment-related outcome differences emerged. In fact, the study was stopped early, after only 46 subjects were enrolled, when improvements in PaO_2:FiO_2 and hospital mortality were observed with hydrocortisone. There is little doubt that clinical trials should be stopped early when there is evidence of harm, but decisions to stop early for benefit must be made cautiously, especially when surrogate endpoints, such as improvement in PaO_2:FiO_2, are primary outcome variables. Though the mortality difference was highly significant (absolute risk reduction of 30% for hospital mortality, p=0.009, NNT=3.3), only one or two deaths in the hydrocortisone group would have been sufficient to tip the balance toward a non-significant mortality difference and in favor of study continuation, rather than early termination of the trial.

This consideration notwithstanding, some important limitations of this study deserve consideration. Because the sample size was small, randomization did not achieve a balance of prognostic factors between groups. Baseline PaO_2:FiO_2 values, CRP levels, and chest radiograph scores were significantly worse in the hydrocortisone group and there was a trend towards more comorbid illness, greater age, and increased initial use of mechanical ventilation in the placebo arm. Although the differences that reached statistical significance would seem to bias against the treatment, these differences do raise concerns that the groups were not similar at the start of the trial. With the current knowledge of the possible beneficial effects of corticosteroids in patients with severe sepsis and adrenal insufficiency [2], one also might question whether the distribution of adrenal insufficiency was different between the placebo and hydrocortisone groups. Unfortunately, no data are provided regarding the adrenal function of these patients. In a study of glucocorticoids, it is almost impossible to keep the investigators completely blinded as white blood cell counts and plasma glucose levels are likely to be elevated in the glucocorticoid group, thereby introducing the potential biases associated with inadequate blinding of the investigators. As acknowledged by the authors, it is difficult in a small study to control for center-specific effects, especially when early study termination precludes any meaningful subgroup analyses. Of particular concern is that individual centers had very different outcomes (center specific mortality ranged from 0% to 36%) and that treatment allocation was not balanced at each site. A smaller randomization block size would have solved this latter issue, but only a larger study could have addressed center-specific effects.

Recommendation

This study suggests that hydrocortisone may improve survival in patients with severe CAP. However, as for any drug therapy, most experts argue for a second study to confirm the results. Given the small sample size and very low mortality rate in the treatment arm, a larger multi-center randomized controlled trial with 90-day mortality [8,9] as the primary end point is needed before hydrocortisone can be recommended as routine therapy for severe CAP.

Competing interests

The authors declare that they have no competing interests.

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