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CORTICUS: The end of unconditional love for steroid use?

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Expanded Abstract

Citation

Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J: Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008, 358:111-124 [1].

Background

Hydrocortisone is widely used in patients with septic shock, even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin.

Methods

Objective: To evaluate the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock — in particular, patients who had had a response to a corticotropin test, in whom a benefit was unproven.

Design: Multi-center, prospective randomized, double-blind, placebo-controlled trial.

Setting: International study involving 52 intensive care units.

Subjects: 499 patients 18 years or older with the diagnosis of septic shock.

Intervention: 251 patients received 50 mg of intravenous hydrocortisone and 248 patients received placebo every 6 hours for 5 days; the dose was then tapered over a 6-day period. A short corticotropin test was performed from blood samples taken immediately before and 60 minutes after an intravenous administration of 250 mcg of cosyntropin prior to administration of hydrocortisone.

Outcomes: Primary outcome was the mortality rate at 28 days in patients who did not have a response to corticotropin. Secondary outcomes included 28-day mortality in corticotropin responders and in all patients; length of stay; reversal of organ failure; and rates of new infection, hypernatremia and hyperglycemia.

Results

Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P=0.69) or in patients who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, P=1.00). Mortality at 28 days included 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) (P=0.51). Shock reversal was quicker in the hydrocortisone group compared to the placebo group. However, there were more episodes of super infection, including new sepsis and septic shock in the hydrocortisone group.

Conclusions

Hydrocortisone did not improve survival in patients with septic shock, either overall or in patients who did not have a response to corticotropin. However, hydrocortisone hastened reversal of shock in all study patients. (ClinicalTrials.gov number, NCT00147004.)

Commentary

The use of corticosteroids in septic shock has been extensively studied. Early investigations determined that high-dose corticosteroids in septic shock are not beneficial and may be harmful [2,3]. Interest was renewed with the observation of hypothalamic-pituitary-adrenal axis dysfunction in patients with septic shock [4-7]. When defined as an increase in plasma cortisol of ≤9 mcg/dl sixty minutes after administration of 250 mcg corticotropin, relative adrenal insufficiency (RAI) occurs in approximately 41-63% of patients with sepsis, is predictive of death [4,7-10] and is associated with a blunted response to vasopressors that can be reversed by hydrocortisone [9,11]. Under this premise, initial studies of stress-dose corticosteroids (200-300 mg hydrocortisone per day) in septic shock were conducted, demonstrating rapid shock reversal [10,12,13]. Subsequently, in a multi-center trial in 300 patients with septic shock refractory to volume resuscitation and vasopressors, Annane and colleagues found that the administration of hydrocortisone 50 mg intravenously every 6 hours and fludrocortisone 50 mcg per day reduced 28-day mortality by 10% in patients with RAI [8]. At the time of publication, this was the most definitive trial of stress-dose steroids in septic shock, greatly influencing intensivists and rapidly became the standard of care [14].

The Corticosteroid Therapy of Septic Shock (CORTICUS) study evaluated the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock, including patients who responded to a corticotropin test, in whom a benefit was unproven. Patients were enrolled if they had clinical evidence septic shock with onset within 72 hours of enrollment. Shock was defined by a systolic blood pressure (SBP) <90 mmHg despite fluid resuscitation or a vasopressor requirement for at least one hour. All patients underwent a corticotropin stimulation test. Somewhat surprisingly, the use of low-dose hydrocortisone had no significant effect on 28-day mortality, regardless of the patients' adrenal responsiveness to corticotropin. The proportion of patients in whom reversal of shock was achieved was similar in the two groups, though this goal was achieved earlier in patients who received hydrocortisone. New infection, hypernatremia and hyperglycemia occurred more frequently in the hydrocortisone group compared to placebo.

CORTICUS is the largest study to date to address the role of corticosteroids in septic shock. Yet, the study has limitations, the most important of which is inadequate power. The study was stopped prematurely due to slow recruitment, termination of funding, and time expiry of the trial drug. As such, only 500 of the intended 800 patients were enrolled. This, coupled with a lower control death rate than anticipated, resulted in the trial having less than 35% power to detect a relative risk reduction of 20% for the primary outcome [15]. Selection bias is another potential limitation. Physicians who were convinced of the benefit of steroids may have been reluctant to withhold this therapy from their sickest patients, thereby excluding the group of patients that theoretically had the most to gain. The lower than expected mortality rate in the control group supports this notion. To better understand the potential influence of this limitation, it would have been useful for the authors to have provided information about the patients who were screened but not included in the study, such as those who were excluded because they were already receiving corticosteroids.

In comparing CORTICUS and the study by Annane and colleagues, there are important methodological differences, which may in part explain their differing findings. In the Annane study, patients were enrolled within eight hours of onset of shock and were still hypotensive (SBP <90 mmHg for at least one hour) despite fluid resuscitation and vasopressor therapy. In contrast, CORTICUS enrolled patients with evidence of shock within the previous 72 hours, as manifest by either hypotension after fluid resuscitation or a vasopressor requirement for at least 1 hour. This led to a disparity in severity of illness between the trials, with Annane and colleagues enrolling a sicker group of patients as measured by SAPS II scores and control group mortality (table).These observations bring into question not only the issue of timing, but also whether sicker patients might be more likely to benefit, as was seen with recombinant human activated protein C [16]. CORTICUS patients more commonly had post-surgical, hospital-acquired, and abdominal infections. Patients with these characteristics may respond differently to steroid therapy than the primarily medical sample studied by Annane and colleagues. Finally, the trials also employed different steroid treatment protocols. The Annane trial used a fixed dose of hydrocortisone along with fludrocortisone for a total of 7 days; whereas in CORTICUS, a tapering dose of hydrocortisone (without fludrocortisone) for a total of 11 days was used. Whether the use of mineralocorticoids is important or a shorter, fixed dose regimen could have made a difference remain important and unanswered questions.

Characteristic	Annane	CORTICUS
SAPS II mean (placebo/treatment)	57/60	49/50
Control group mortality	61%	32%
Corticotropin non-responders	77%	47%
Admission category - medical	60%	35%
Hospital-acquired infection	21%	47%
Post-surgical infection	16%	61%
Abdominal infection	16%	49%

Table 1: Comparison of patient characteristics in CORTICUS and the study by Annane and colleagues.

There are two additional studies addressing the use of corticosteroids in septic shock that should be mentioned. The Combination of Corticotherapy and Intensive Insulin Therapy for Septic Shock (COIITSS) study is completed, but not yet published [17]. This study used a factorial design in 508 adults with septic shock to simultaneously compare hydrocortisone alone versus hydrocortisone plus fludrocortisone and intensive insulin therapy versus

conventional glucose control. The other study, Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHS), is ongoing [18]. APROCCHS aims to compare the efficacy and safety of recombinant human activated protein C to that of low dose of corticosteroids and to investigate the interaction between these drugs in 1280 adults with septic shock.

Recommendation

Pending results of adequately powered studies, it would seem appropriate to reserve corticosteroids for patients with septic shock whose blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy [19]. There are no data defining what constitutes adequate fluid resuscitation or what level of vasopressor support should trigger initiation of corticosteroids. Furthermore, the corticotropin stimulation should not be used to determine which patients should receive steroid therapy for septic shock. Given the potential risks of infection, hyperglycemia, and myopathy, discontinuing corticosteroids should be considered if patients fail to respond to treatment.

Competing interests

The authors declare no competing interests.

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