No Mortality Benefits with Hydrocortisone Therapy in Patients with Septic Shock

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.

Study Overview

Objective. To determine whether hydrocortisone administration improves survival in patients with septic shock.

Design. Multicenter, randomized, double-blind, placebo-controlled trial.

Setting and participants. 499 patients aged ≥ 18 years with septic shock. Patients with a life expectancy < 24 hours, immunosuppression, or prior recent steroid use were excluded. Patients were randomized to receive either 50 mg of intravenous hydrocortisone or placebo every 6 hours for 5 days, followed by a 6-day taper. Patients underwent laboratory testing, including corticotropin stimulation testing, prior to randomization.

Main outcome measure. All-cause mortality at 28 days in patients who did not respond to corticotropin (an increase in serum cortisol of ≤ 9 μg/dL). Secondary endpoints included rates of death: (1) in all patients and in those who responded to corticotropin at 28 days, (2) in the intensive care unit (ICU) and in the hospital, and (3) at 1 year as well as ICU and hospital length of stay (LOS).

Main results. 251 patients received hydrocortisone and 248 patients received placebo. 233 patients did not respond to corticotropin (125 in the hydrocortisone group, 108 in the placebo group). There were no significant differences in 28-day mortality among patients who received hydrocortisone versus those receiving placebo (34.3% vs. 31.5%; P = 0.51), between patients in the hydrocortisone and placebo groups who responded to corticotropin (28.8% vs. 28.7%; P = 1.00), and between patients in the hydrocortisone and placebo groups who did not respond to corticotropin (39.2% vs. 36.1%; P = 0.69). There were no significant differences between patients receiving hydrocortisone versus placebo in the following secondary outcome measures: death in ICU, death during hospitalization, death at 1 year, and ICU and in-hospital LOS. Median time to reversal of shock (among patients whose shock was reversed) was shorter in patients receiving hydrocortisone versus those receiving placebo (3.3 vs. 5.8 days; P < 0.001). Hydrocortisone administration was significantly associated with higher risk of new septic shock (relative risk [RR], 2.78 [95% confidence interval {CI}, 1.02–7.58]), hyperglycemia (RR, 1.18 [95% CI, 1.07–1.31]), and hypernatremia (RR, 1.58 [95% CI, 1.13–2.22]).

Conclusion. Hydrocortisone does not affect survival rates in patients with septic shock, regardless of their response to corticotropin stimulation testing. Although hydrocortisone may accelerate the reversal of shock, it was associated with adverse events, including new sepsis.

Commentary

The cortisol response to exogenous corticotropin (the "cort stim" test) has well-established prognostic value in septic shock—mortality among patients with a normal corticotropin response is significantly lower than in patients with an abnormal response (26% vs. 83% at 28 days) [1]. This observation has led to the widespread use of cortisol replacement, most commonly with hydrocortisone, as adjunctive therapy in septic shock, with the greatest expected clinical benefit among patients with an abnormal response to corticotropin [2]. The use of corticosteroids as adjunctive therapy in septic shock has been advocated in multiple meta-analyses [3–5] and published guidelines [6].

The current investigation by Sprung and colleagues examines the effect of a commonly used low-dose steroid regimen in a broad-based population of patients with septic shock. Compared with placebo, hydrocortisone therapy provided no benefits for survival, regardless of patient response to corticotropin stimulation testing. There were also no benefits for several measures of length of recovery, and hydrocortisone was associated with higher rates of known complications of steroid therapy (ie, infection, hyperglycemia, hypernatremia). These findings differ with those of an influential prior trial that showed a mortality benefit with steroid replacement among patients with an abnormal corticotropin response [2]. Unlike the study by Sprung et al, patients enrolled in the prior trial received fludrocortisone in addition to hydrocortisone and were required to have persistent hypotension despite 1 hour of fluid and vasopressor administration.

Despite the importance of Sprung et al's findings for in-

tensive care providers, some important limitations exist. First, because study enrollment fell short of its prespecified 800 patient target, its power to detect a mortality benefit was lower than planned. However, the nonsignificant observed trend in mortality rates was toward higher mortality among patients receiving hydrocortisone. This suggests that failure to detect a survival benefit with hydrocortisone was not the result of insufficient statistical power. Second, 21 patients (4.2%) received open-label steroids; however, this low rate makes significant confounding a less likely explanation for the observed results. Finally, the current study did not include an arm for patients with blood pressure unresponsive to fluids and vasopressor therapy. Such patients constitute a population in which steroid therapy is most strongly recommended, and their identification would have allowed a more direct evaluation of current guidelines for the treatment of septic shock [6].

Applications for Clinical Practice

The common practice of administering hydrocortisone as adjuvant therapy to the general population of patients with septic shock should be questioned, as should the common practice of using corticotropin response to guide steroid therapy.

—Review by Mark W. Friedberg, MD, MPP

References

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