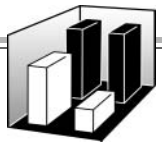

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Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock

Annane D, Sebille V, Charpentier C, *et al.*: **Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.** *JAMA* 2002, **288:**862–871.

Rating: •Of importance.

Introduction: Severe sepsis has a high mortality despite the substantial elucidation of much of its pathophysiology in recent years. Many trials of drugs considered to be likely antagonists of the evolution of the syndrome have yielded disappointing results, which has been the fate of high doses of corticosteroids administered for short periods. However, the presence of diminished adrenal reserve, or relative adrenal insufficiency, was shown to be frequent in septic shock and associated with a higher mortality than in patients able to respond better to corticotropin [1]. Those observations resulted in interest in corticosteroid replacement therapy for longer periods in septic shock. Such studies have demonstrated improved catecholamine pressor responses in patients with septic shock administered low doses of hydrocortisone, especially in those with relative adrenal insufficiency [2].

Aims: The goal of this placebo-controlled study was to determine whether low doses (replacement therapy) of hydrocortisone and fludrocortisone would be able to improve 28-day survival in patients with septic shock, particularly in patients demonstrated to have relative adrenal insufficiency.

Methods: The study was a placebo-controlled, randomized, double-blind trial conducted in 19 intensive care units in France between 1995 and 1999 on patients aged at least 18 years. Criteria for enrollment were specifically defined and, in general, included all of the following: good evidence of infection; fever or hypothermia; tachycardia; hypotension unresponsive to fluid replacement and pressor agents; poor urine output or lactic acidosis or evidence of poor pulmonary function; and need for mechanical ventilation. Subjects were administered a short corticotropin test using a 250-μg intravenous bolus of tetracosactrin, with blood samples for cortisol determination taken just before and 30 and 60 minutes after the test. They were then randomized into the steroid treatment (hydrocortisone 50 mg intravenously every 6 hours and fludrocortisone 50 μg through a nasogastric tube daily for 7 days) or placebo groups within 8 hours of onset of septic shock. Exclusions included pregnancy, acute myocardial infarction, pulmonary embolism, advanced cancer or AIDS, and contraindication or formal indication for steroids.

Results: During the study period, 1326 patients were screened and 300 who met the inclusion criteria were enrolled, including 149 in the placebo group and 151 in the corticosteroid treatment group. One patient from the corticosteroid group was excluded from analysis because of withdrawal of consent. There were 229 patients (76%) who did not respond to the corticotropin stimulation test (considered to have relative adrenal insufficiency with a cortisol incremental response of 9 μg/dL or less) and 70 responders (24%). The placebo and corticosteroid groups were well-balanced regarding general characteristics, severity of illness, and appropriate administration of antibiotics. However, the mean time to initiate appropriate antibiotics in the nonresponder group was approximately 5 to 6 hours and approximately 9 hours in the responder group. Each center randomized 1:1 into the two treatment groups. At 28 days, there were 73 deaths (63%) in the nonresponder group out of 115 who received placebo and 60 deaths out of 114 (53%) who received steroids (adjusted odds ratio [0R] = 0.54; 95% confidence interval [CI] = 0.31–0.97; $P = 0.04$). After 1 year of follow-up there were 88 deaths (77%) in the placebo group and 77 deaths (68%) in the steroid group (adjusted OR = 0.57; 95% CI = 0.31–1.04; $P = 0.07$). Among responders at 28 days, there were 18 deaths (53%) out of 34 in the placebo group and 22 deaths (61%) out of 36 who received steroids (adjusted OR = 0.97; 95% CI = 0.32–2.99; $P = 0.96$). At 1 year there was no significant effect of steroid therapy on mortality in the responder group. Among the nonresponders, vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and 65 patients (57%) in the steroid group (hazard ratio = 1.91; 95% CI = 1.29–2.84; $P = 0.001$). In that regard, there was no significant difference between the treatment groups in the responders. Adverse events were similar in the placebo and steroid treatment groups.

Discussion: The study indicated that in catecholamine-dependent septic shock in patients with relative adrenal insufficiency, corticosteroid replacement therapy for 7 days can safely and significantly reduce short-term mortality. In that group, one additional life could be saved at 28 days for every seven patients treated with corticosteroids. The study confirms earlier observations in patients with septic shock showing the beneficial effects of low doses of hydrocortisone on vascular responsiveness to catecholamines [3]. The usefulness of a short corticotropin test in early septic shock to identify patients who would benefit from the steroid therapy was also demonstrated. The addition of fludrocortisone to hydrocortisone was considered potentially beneficial because primary adrenal insufficiency could not be ruled out. It is suggested that all patients with catecholamine-dependent septic shock be administered this therapeutic regimen immediately after the short corticotropin stimulation test is performed. The treatment may be withdrawn in cases in which test results indicate an adequate response to the corticotropin but should continue for 7 days in the nonresponder group.

Editor's comments

Animals and humans with infectious diseases fare better when they have normal adrenal function compared to those that have chronic hypo- or hyperadrenalism [4]. It has been repeatedly observed that the hypothalamic-pituitary-adrenal axis is generally stimulated by acute infectious diseases, especially in the early phases, associated with modest elevations of plasma cortisol with the obliteration of the normal diurnal variation in adrenal glucocorticoid secretion [4]. One can speculate that the pathophysiology is likely the result of proinflammatory cytokines stimulating the hypothalamus. Older studies provided less information on adrenal function in infection as it progressed to a more severe state. However, limited data indicated very high levels of glucocorticoids in some severely ill patients together with parameters suggesting decreased clearance or degradation of glucocorticoids [4]. Children with adrenal hemorrhagic necrosis associated with acute meningitis had plasma glucocorticoid levels that were usually low [5]. In recent years, it has been shown that a state of relative adrenal insufficiency occurs frequently in septic shock [1], which (one can speculate) may reflect diminished function of cells in the hypothalamic-pituitary-adrenal axis, resulting from mitochondrial dysfunction with end-organ failure caused by the septic syndrome [6].

The interesting and well-designed study presented here indicates that most patients with severe septic shock have relative adrenal insufficiency and suggests that short-term (28-day) survival can be modestly improved for this group, although 50% of patients die if they are administered low (replacement) doses of a glucocorticoid and a mineralocorticoid relatively early in their course and continued for 1 week. However, the 1-year survival of nonresponders administered this treatment compared to placebo was less impressive. Although the study involved 19 centers, each center randomized subjects equally into the treatment and placebo groups, thus minimizing care differences among the different intensive care units. There was a substantial delay in administering appropriate antibiotics after the diagnosis of severe sepsis, which was greater for the responder group. Perhaps a potential beneficial effect of steroid therapy in the latter group was blunted by that delay. Additional studies are needed to confirm the observations in this study, to determine whether similar results will be found in less severe forms of sepsis, to work out the optimal dose of glucocorticoids, and to examine whether there is a detrimental effect of these agents when administered to patients who do not exhibit relative adrenal insufficiency in sepsis [7]. The treatment of severe septic shock with low doses of steroids as administered in this study is warranted and continued for 7 days only when poor cortisol response in the corticotropin test is documented. It must be determined how this regimen will interact with other strategies that also appear to have benefit in some patients with sepsis (namely, glucose control with insulin and the use of activated protein C in septic shock) [7].

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