CJEM Journal Club

Steroids for patients in septic shock: the results of the CORTICUS trial

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Clinical question
What is the role of steroids in septic shock in the emergency department?
Article chosen
Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008;358:111-24.
Study objective
To assess the safety and efficacy of low-dose hydrocortisone therapy for patients with septic shock and to compare outcomes based on response to corticotropin testing.

Keywords: sepsis, shock, steroids

BACKGROUND

Sepsis accounts for 4 of 1,000 emergency department visits in the United States and occurs in approximately 2% of hospitalized patients, with a mortality rate of 20 to 50%.[1–7] Efforts to decrease mortality have focused on a number of interventions, including the use of corticosteroids for treatment of relative adrenal insufficiency, which is thought to complicate approximately 60% of septic shock presentations.[8] Studies that have evaluated the use of short-course corticosteroids in patients with septic shock have yielded mixed results in terms of mortality outcome data and have not been definitive in recommending which patients should receive the therapy.

STUDY DESIGN AND PATIENT POPULATION

The Corticosteroid Therapy of Septic Shock (CORTICUS) study was a prospective, multicentred, randomized, double-blind, placebo-controlled trial.[9] Patients were recruited from 52 intensive care units (ICUs) in nine countries from March 2002 to November 2005. Patients were 18 years of age or older with clinical evidence of infection, evidence of systemic response to infection, and hypoperfusion or organ dysfunction attributable to sepsis. The onset of shock had to occur within 72 hours of admission and was defined as a systolic blood pressure of < 90 mm Hg despite adequate fluid resuscitation or the need for the infusion of vasopressor medications for longer than 1 hour. Patients were excluded if they had a preexisting illness with poor prognosis, were expected to die within 24 hours, were immunosuppressed, had used long-term corticosteroids in the previous 6 months, or had used short-term steroids in the previous 4 weeks. Randomization occurred in a 1:1 fashion in blocks of four and was carried out using a computerized random

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number generator where study drugs appeared similar, and all study participants and administrators were blinded to treatment assignment.

Patients were randomized to receive either hydrocortisone or placebo as a 50 mg intravenous bolus every 6 hours for 5 days and then tapered to 50 mg every 12 hours for 3 days and finally 50 mg every 24 hours for an additional 3 days. All patients were to undergo a corticotropin stimulation test prior to initiation of therapy.

OUTCOME MEASURES

The primary end point was 28-day all-cause mortality in patients who did not respond to corticotropin (defined as a change of $\leq$ 9 μg/dL or 248 nmol/L in cortisol after a 250 μg cosyntropin stimulation test). Secondary end points were mortality in those patients who responded to corticotropin and in the overall population at various time intervals including in the first 28 days, in the ICU, during hospital admission, and at the 1 year follow-up. Additional secondary end points included organ failure resolution, shock resolution, and ICU and hospital lengths of stay. Safety was monitored by the collection of adverse event data, including rates of superinfection.

A power calculation, estimating a sample size of 800 patients, was performed to detect a 10% mortality difference from a projected mortality rate of 50% in patients who lack a response to corticotropin (40% of total). However, the trial was stopped after 500 patients were enrolled, reaching only 62.5% of the sample size, owing to "slow recruitment..., termination of funding and time expiry of the study drug."[9]

RESULTS

After enrolment of 500 patients, 251 were assigned to receive hydrocortisone (1 withdrew consent) and 248 received placebo. Two hundred thirty-three patients (46.7%) did not have a response to corticotropin. There was no difference in 28-day mortality in patients receiving hydrocortisone versus placebo in nonresponders (39.2% v. 36.1%), responders (28.8% v. 28.7%), or all patients (34.3% v. 31.5%). These differences were also not present between any of the groups when looking at mortality rates during ICU stay, during total hospitalization, or at 1 year. The overall length of stay was similarly unaffected between groups. Although those in the hydrocortisone group with persistent hypotension had an 11.3% mortality reduction compared to those hypotensive patients receiving placebo, this was not statistically significant ($p = 0.28$).

Reversal of shock occurred at similar rates in patients receiving hydrocortisone versus placebo whether or not they responded to corticotropin and overall. However, in those who did reverse their shock, reversal occurred more quickly in patients treated with hydrocortisone compared to placebo in all three groups: 3.3 versus 5.8 days overall, 2.8 versus 5.8 days in those who responded to corticotropin, and 3.9 versus 6.0 days in those who did not respond.

In the hydrocortisone group, there was an increased incidence of superinfection, including new sepsis or septic shock, with a combined odds ratio of 1.37 (95% CI 1.05 to 1.79), as well as an increased incidence of hyperglycemia and hypernatremia. The prevalence of other adverse events was similar, including the rate of critical illness polyneuropathy.

COMMENTARY

The emergency department treatment of septic patients has been the focus of considerable attention. The Surviving Sepsis Campaign guidelines published in 2004[10,11] and widespread adaptation of early goal-directed treatment protocols[12] have been paramount in establishing benchmarks for the evidence-based treatment of septic patients. The question of whether to initiate treatment with corticosteroids in patients with septic shock continues to be an area of considerable controversy. Based on available data at the time and including results from the CORTICUS trial, the current recommendations from the *Canadian Journal of Emergency Medicine* clinical practice guidelines[13] and the Surviving Sepsis Campaign[14] are to administer steroids to septic shock patients who have refractory hypotension despite adequate fluid resuscitation and vasopressor therapy (D and 2C recommendations, respectively).

The CORTICUS trial was one of six randomized controlled trials investigating whether hydrocortisone in sepsis improves mortality in moderate-dose administration (200–300 mg/d). A meta-analysis of data from these trials favours shock reversal but demonstrates no mortality benefit.[15] A further meta-analysis, which included 17 randomized and 3 quasirandomized trials, did not demonstrate a difference in all-cause mortality at 28 days.[16] However, a subgroup analysis of those

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trials looking at prolonged low-dose corticosteroid treatment did demonstrate a 28-day mortality reduction from 44.1% to 37.5% (95% CI 0.72–0.97) in those treated with hydrocortisone.

In part, the goal of these meta-analyses was to attempt to determine how to reconcile the conflicting results of the CORTICUS study with the only other reasonably powered study for mortality: the French multicentre study by Annane and colleagues, which included 300 patients with refractory septic shock who were randomized to receive hydrocortisone and fludrocortisone or placebo for 7 days.[17] In this study, the group that did not respond to the corticotropin stimulation test had a 10% reduction in 28-day mortality when treated with corticosteroids. The difference in outcome when compared to the CORTICUS trial is likely a consequence of a number of different factors. The patients in the Annane and colleagues trial had higher organ dysfunction scores, had greater hemodynamic instability, were enrolled earlier (within 8 hours v. 72 hours), and were more likely to be surgical patients. All of these factors point to the need for proper patient selection to determine who might benefit from the administration of steroids.

It is possible that the lack of mortality benefit in the CORTICUS trial may be due to confounding variables and not the failure of the hydrocortisone administration. The study experienced significant difficulty in recruiting its target sample size. This may have been due to the fact that clinicians were unwilling to randomize their patients to the possibility of not receiving steroids, which at the time was thought to confer a significant survival advantage based on the Annane and colleagues data.[17] In addition, newer treatment strategies such as early goal-directed therapy may have accounted for the difference in placebo mortality (61% in the Annane and colleagues study v. 32% in CORTICUS) and could also have affected the response to corticosteroids.

One of the major limitations of the CORTICUS trial was that it was stopped early owing to slow recruitment, termination of drug funding, and time expiry of the trial drug. This resulted in only 62.5% of the a priori sample size, possibly resulting in failure to identify a treatment effect. Although the study was not stopped early because of apparent benefit, concern must be raised over the interpretation of data gathered from any truncated trial, for any reason, particularly when the target sample size was not achieved. Stopping trials early for apparent benefit typically overestimates the treatment effect.[18,19] Randomized controlled trials stopped early for reasons other than benefit might share some characteristics with those stopped because of an apparent benefit; however, their implications are very different.[20] Trials stopped early because of harm or futility tend to result in decreased use or prompt discontinuation of useless or potentially harmful interventions. In contrast, trials stopped early for benefit may result in the hasty institution into practice. Similar to both situations are the questionable magnitude and plausibility of their treatment effects and the reasons behind their premature arrest.

It is often difficult to interpret the results of such a truncated trial. Just as stopping a trial early for apparent benefit might overestimate the treatment effects, stopping early because of apparent lack of benefit might underestimate the treatment effect. This is especially concerning given the lack of power achieved in the CORTICUS trial and the lower control death rate, which suggests that either selection bias was introduced or the sickest patients were not enrolled. It is plausible that sicker patients are more likely to benefit, but this effect may not have been seen owing to early termination.

CONCLUSION

The results of the CORTICUS study provided no additional insights into the role of steroids for septic shock for emergency physicians treating these patients in the first hours of this process. The study did not recruit its predetermined sample size. Its negative results arose from a study population who may have had up to a 72-hour delay in the initiation of steroids. Its results therefore are probably not applicable to the emergency department setting. In patients with septic shock, current data suggest that those who receive corticosteroids may benefit from a faster resolution of hypotension if corticosteroids are administered early (within the first 8 hours). This potential benefit has to be weighed against the possible increase in superinfection and recurrent shock.

In the emergency department, steroids should be administered to septic patients who remain hypotensive despite aggressive volume resuscitation and vasopressors. Hydrocortisone 50 mg IV would be a common initial dose with a cumulative 24-hour dose of 200 to 300 mg given three to four times daily.

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Competing interests: None declared.

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