Why the Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (ADRENAL) Trial Did Not Show a Difference in Mortality

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Key Words: corticosteroids; mortality; septic shock

Two recent randomized controlled trials Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (ADRENAL) and Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) have reported on the role of corticosteroids in patients with septic shock (1, 2). The ADRENAL trial (n = 3,800) investigated the role of 200 mg/d of hydrocortisone for 7 days compared with placebo and reported no significant difference between groups with respect to 90-day mortality (27.9% vs 28.8%). The APROCCHSS trial (2) (n = 1,241) examined the effect of 200 mg/d of hydrocortisone, combined with oral fludrocortisone for 7 days compared with placebo and reported improved 90-day mortality in the intervention group (43.0% vs 49.1%). The difference in the primary outcome between the trials has generated substantial debate. This review explores whether the key differences between the two trials could have impacted on the primary outcome.

WERE THE TRIAL POPULATIONS DIFFERENT?

Although the two trials had several design features and baseline characteristics in common, there were key differences (**Table 1**). The impact of these differences is discussed in detail below.

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Supported, in part, by an National Health and Medical Research Council of Australia project grant 1162182 and a Medical Research Future Fund Practitioner Fellowship.

Dr. Venkatesh received support for article research from National Health and Medical Research Council of Australia Health Research Council of New Zealand. Dr. Cohen disclosed that he does not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000003834

Etomidate Exposure

Exposure to etomidate (a known adrenal suppressant) pre randomization was an exclusion criterion in ADRENAL, but not the APROCCHSS trial. Etomidate use was a key confounding factor in the Ger-inf-05 (3) and the Corticosteroid Therapy of Septic Shock (CORTICUS) trials (4), the two earlier pivotal trials of low dose steroids.

Baseline Sickness Severity

The illness severity between the two trials is not directly comparable. ADRENAL reported Acute Physiology and Chronic Health Evaluation (APACHE) II scores, whereas the APROCCHSS reported the Simplified Acute Physiology Score and Sequential Organ Failure Assessment scores. Baseline pressor requirements, plasma lactate concentrations, and need for renal replacement therapy were higher in the APROCCHSS trial, but a greater proportion of patients were mechanically ventilated in the ADRENAL trial. The impact of sickness severity on the effect of corticosteroids is discussed in detail below.

Predominance of Pulmonary Sepsis

Data from several studies and meta-analyses suggest that corticosteroids may have a beneficial effect on patients with community-acquired pneumonia admitted to an ICU (5–7). The APROCCHSS trial had a higher proportion of patients with pulmonary sepsis compared with ADRENAL (59% vs 35%). Whether this may have contributed to the differences in the primary outcome is unclear. In a predefined subgroup of the ADRENAL cohort, comparing pulmonary versus nonpulmonary primary site of sepsis, there was no significant effect of the trial regimen on the primary outcome. A subgroup analysis of the APROCCHSS trial patients with pulmonary sepsis will inform this debate.

MODE OF HYDROCORTISONE ADMINISTRATION

Hydrocortisone was administered as a continuous infusion in ADRENAL and as intermittent boluses in the APROCCHSS trial. Administration of hydrocortisone by infusion is associated with attenuation of the inflammatory response, lower vasopressor requirements, greater proportion of shock reversal,

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TABLE 1. Key Differences in Trial Design and Baseline Characteristics Between ADRENAL and APROCCHSS

	ADRENAL (n = 3,800)	APROCCHSS (n = 1,241)
Trial Design	Parallel Group RCT	2 × 2 Factorial Design Converted to a Parallel Group RCT
Inclusion-exclusion criteria		
Mechanical ventilation as an inclusion criterion	Yes	No
Minimum duration of continuous pressor therapy before enrolment	4 hr	6 hr
Minimum dose of pressor therapy	Not mandated	0.25 μg/kg/min of noradrenaline
Etomidate as an exclusion criterion	Yes	No
Sources of sepsis, %		
Proportion of patients with medical sepsis	68.5	81.7
Pulmonary source of sepsis	35.1	59.3
Abdominal source of sepsis	25.5	11.4
Baseline therapies, %		
Mechanical ventilation	99.8	91.8
Proportion of patients receiving vasopressin	16.2	0.08
Proportion of patients receiving renal replacement therapy	12.7	27.5
Interventions		
Hydrocortisone	Infusion	Bolus
Fludrocortisone	No	Yes

ADRENAL = Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock, APROCCHSS = Activated Protein C and Corticosteroids for Human Septic Shock, RCT = randomized controlled trial.

and fewer adverse metabolic effects (8) and in accord with current clinical practice recommendations for septic shock (8, 9). A systematic review found no influence of the method of hydrocortisone administration on outcome (10). As both trials used identical total daily doses, and there was evidence of other key pharmacological effects such as reversal of shock, it is unlikely that the mode of administration was a significant contributor to the observed difference in primary outcome.

FLUDROCORTISONE

A key difference between the two trials was the use of fludrocortisone in the APROCCHSS trial. The rationale for the use of fludrocortisone was the possibility of concomitant primary adrenal insufficiency and down-regulation of the mineralocorticoid receptor in septic shock (11). It is questionable whether the addition of fludrocortisone to hydrocortisone would confer additional benefit.

In vitro the mineralocorticoid receptor has an equal affinity for both mineralocorticoids and glucocorticoids and would be expected to be activated by circulating cortisol, normally found in far higher concentrations than aldosterone (12). The intracellular isoenzyme, 11-beta-hydroxysteroid dehydrogenase 2 (11-βHSD2), provides homeostatic regulation by converting cortisol to inactive cortisone, thus preventing excess mineralocorticoid receptor activation from cortisol. At doses of hydrocortisone used in septic shock, plasma cortisol concentrations approximate 3,500 mmol/L (13) which would be anticipated to overload the isoenzyme and activate the mineralocorticoid receptor. This is also the basis for the recommendation that in primary adrenal crisis, a daily dose of 50 mg or more of hydrocortisone (equivalent to 0.1 mg of fludrocortisone) provides sufficient mineralocorticoid activity such that concomitant fludrocortisone is not required (14).

Besides, fludrocortisone has a short plasma half-life (1.4 hr) (15) and its oral absorption is impaired in critically ill patients (16). A randomized trial comparing hydrocortisone plus fludrocortisone versus hydrocortisone alone in septic shock did not demonstrate any treatment effect on mortality although the trial was underpowered (17). A definitive answer on the role of fludrocortisone would only be achieved by an adequately powered randomized trial.6

ARE STEROIDS MORE EFFICACIOUS IN SEVERE SEPTIC SHOCK?

The demonstration of mortality benefit in the APROCCHSS trial raises the question whether corticosteroids are more efficacious in patients with severe septic shock. There is no biological basis to suggest that an arbitrary minimum dose of vasopressors is necessary for corticosteroids to be clinically effective, given the inter- and intraindividual variability in

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vasopressor responsiveness. There was concordance between the ADRENAL and the APROCCHSS trials with respect to important patient-centered secondary outcomes—shock reversal, days alive and free of ICU, and 28-day mortality—counteracting the argument that steroids are effective only in a sicker cohort. Analysis of the primary outcome in the ADRENAL trial in the prespecified subgroups of greater sickness severity (APACHE > 25, n = 1625) and severe shock (noradrenaline dose > 15 μg/min, n = 1654) did not reveal a different treatment effect on mortality. The primary outcome was consistent across all geographic regions including those with higher 90-day mortality. These suggest consistency of treatment effect across both mild and the severe end of the illness spectrum.

VASOPRESSIN USAGE

The proportion of patients in whom vasopressin was used in the APROCCHSS cohort was 0.08% as opposed to 16.2% in ADRENAL. This raises the question whether the presence of concomitant vasopressin may diminish the efficacy of corticosteroids. Vasopressin leads to adrenocorticotropic hormone release and corticosteroids restore cytokine-mediated downregulation of vasopressin receptors. The interaction between vasopressin and corticosteroids is complex with conflicting evidence in animal models (18, 19). The finding of a favorable interaction between corticosteroids and vasopressin on mortality has not been consistently observed in clinical trials (20, 21). The rationale for the use of vasopressin in septic shock is strong—deficiency of vasopressin, improvement of blood pressure, and improved renal function. To date, there is no biological basis or clinical evidence to support the hypothesis that vasopressin diminishes the efficacy of corticosteroids.

COULD VARIABLE SENSITIVITY TO THE EFFECTS OF CORTICOSTEROIDS INFLUENCE THE OUTCOME?

Response to corticosteroids in critically ill patients may be variable. Altered expression of glucocorticoid receptor splice variants, observed in patients with septic shock, may result in corticosteroid resistance (22). Altered activity of the 11-βHSD isoenzymes may also contribute to this effect (23). Differences in genome-wide expression patterns in response to sepsis may affect mortality. Adult patients expressing an immunocompetent expression phenotype had a higher mortality when treated with corticosteroids than those with an immune-supressed expression phenotype (24). In children in whom glucocorticoid receptor signaling genes were repressed had a higher mortality when treated with corticosteroids than those whose expression pattern was different (25). These serve to highlight the clinical and biological heterogeneity of septic shock.

The ADRENAL trial had high internal validity, was multicenter (69 sites) and multinational (five countries), allowing generalizability of results. The statistical analysis plan was published before unblinding, analysis adjusted for stratification and multiplicity, and sensitivity analyses conducted with six covariates. The larger sample size of the ADRENAL trial ensured that the risk of a Type 1 error was minimized. A significant treatment effect in ADRENAL observed at the first interim analysis (n = 950) was followed by a return to the null result as the trial progressed to full enrolment (n = 3,800). The lack of a significant treatment effect on mortality was consistent at all three time points—Day-28, Day-90, and Day-180 (1, 26).

Prior to the ADRENAL and the APROCCHSS trials, international surveys suggested that clinicians used low dose steroids largely for hemodynamic benefit and initiated steroids at various threshold doses of vasopressors indicating substantial clinical uncertainty (27). The ADRENAL trial used a pragmatic design and did not stipulate a minimum dose of pressors for initiating steroid therapy thus replicating current practice. The results of the ADRENAL study are also consistent with those of the Ger-Inf-05 and the CORTICUS trials. In both these trials, there were no significant differences in overall mortality at 28 days or 1 year between the treatment groups. The finding of improved survival in the steroid arm among corticotropin nonresponders in the Ger-Inf-05 trial was not reproduced in the APROCCHSS study.

The reasons for the differences in the primary outcome between the ADRENAL and the APROCCHSS trials remain to be elucidated. Based on the evidence from these trials and subsequent meta-analyses, it can be concluded that hydrocortisone is safe, results in faster resolution of shock, reduced duration of mechanical ventilation and ICU length of stay. Recognizing corticosteroid-responsive phenotypes based on genetic markers and delineating the role of fludrocortisone in a robust clinical trial might provide further insight into understanding the mechanisms of benefit of steroids in patients with septic shock.

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