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Shock reversal with hydrocortisone: a double blind trial

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Keywords

Hydrocortisone, septic shock

Comments

The use of hydrocortisone in septic shock is gaining wider acceptance in everyday ITU clinical practice and this paper adds further evidence for a beneficial role, albeit not one of improving survival. It was, however, a relatively small trial, with only 40 patients entered over 3 years in a 20 bed unit. This may have been due to the inclusion criteria, and presumably the case mix in that unit. The inclusion criteria are in fact confusing, with the authors stating that only patients on vasopressors, in which they include epinephrine, and with a high cardiac index were included but that the hyperdynamic state had to be present in the absence of positive inotropes, in which they also include epinephrine. Another quibble is that the primary end point, ie shock reversal, was defined as being off vasopressors. In the case of dopamine, a dose of less than 6 mg/kg/min was considered not to represent vasopressor support. This is contentious, with recent evidence suggesting that such selective effects of dopamine related to dose are not valid in critically ill patients (Juste RN, *et al. Intens Care Med* 1998, **24**:1217-1220).

Lastly it is surprising that no reference is made in the discussion to the study of Bollaert *et al* published last year in the same journal (*Crit Care Med* 1998, **26**:645-650). This was of the same size, using similar doses of hydrocortisone, although in a simpler regime but with similar findings.The case for the routine use of hydrocortisone in septic shock is not yet clear cut, although the evidence is encouraging. A large, multicenter trial is clearly needed.

Introduction

Hypercortisolemia (mainly resulting from pituitary-adrenal axis activation) associated with septic shock, tends to suppress the immune system, thus protecting the host from inappropriate immune responses. The syndrome of relative adrenocortical insufficiency during septic shock has been proposed in recent years, based on a number of studies of patients with septic shock. This has lead to proposals for replacement therapy clinical trials using stress doses of hydrocortisone. To date, this approach has not been investigated in a modern intensive therapy unit (ITU).

Aims

To analyse the effects of stress doses of hydrocortisone on the length of vasopressor support required in patients with septic shock.

Methods

A total of 40 patients meeting the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) criteria for septic shock, were prospectively entered into the study. Initial severity of illness was assessed using the acute physiology and chronic health evaluation (APACHE) II and the simplified acute physiology score (SAPS) II scoring systems. The patients were randomly allocated to two groups, one receiving the hydrocortisone dosing regimen (initial dose of 100 mg over 30 min then continuous infusion of 0.18 mg/kg/h) the other receiving placebo (0.9% NaCl). When septic shock had been reversed, the hydrocortisone dose was reduced to 0.8 mg/kg/h and kept constant for 6 days. Upon successful treatment of the underlying infection, the hydrocortisone infusion was decreased in 24 mg/day steps. Hemodynamic values were measured, together with venous and arterial blood gasses, at 0, 12, 24, 36, and 48 h, thereafter at 24 h intervals. Right ventricular function, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were also measured. The primary end point of this study was the time to shock reversal (defined as cessation of vasopressor support) with secondary study end points being the evolution of hemodynamics and the multiple organ dysfunction syndrome (MODS). All patients were followed until they were either discharged from the ITU, or they died.

Results

Of the 40 patients, 30 survived. Of the 10 deaths, four were from the hydrocortisone group. One year after the study, 15 patients from the hydrocortisone group and 14 from the placebo group were still alive. Septic shock reversal was achieved in 18 patients from the hydrocortisone group and in 16 patients from the placebo group. Patients in the hydrocortisone group also had significantly reduced vasopressor support times (median 2 versus 7 days for the placebo group). The hydrocortisone group also showed a trend towards faster resolution of organ dysfunction. This trend was most noticeable in the cardiovascular, respiratory and central nervous systems. This faster resolution was associated with lowered mean duration of mechanical ventilation in the hydrocortisone group (18 versus 38 days). The length of stay in the ITU was also decreased in the hydrocortisone group (27 versus 44 days). Reversible side effects of the hydrocortisone treatment consisted of increases in serum sodium concentrations, blood glucose, urea, nitrogen, and liver enzymes.

Discussion

The authors conclude that the stress doses of hydrocortisone used led to a significant shortening of the time to reversal of septic shock; defined in this study as losing the need for vasopressor treatment, although overall reversal of shock and death rate was not significantly affected. An increase in MAP and systemic vascular resistance (SVR) was noted in the treatment group and possible mechanisms by which the vasopressor unresponsiveness, characteristic of septic shock, might be reversed are discussed. Overproduction of nitric oxide may be partly to blame, a theory supported by work using NG monomethyl-L-arginine (L-NMMA), a nitric oxide synthase inhibitor, in human septic shock, where similar hemodynamic changes to those demonstrated in this study were seen. Indeed inhibition of expression of vascular endothelial nitric oxide synthase by glucocorticoids has been shown by others. A further mechanism may be related to the sodium retention caused by hydrocortisone, a mineralocorticoid effect, which can lead to hypertension in humans. A raised sodium concentration was noted in the treatment group. It is suggested that the observed lower right ventricular end diastolic volumes seen in the hydrocortisone group, despite higher pulmonary resistance, may indicate that right ventricular dilation is due more to systemic inflammation than pulmonary resistance or afterload.An attempt was made to evaluate the effect of hydrocortisone on the course of organ dysfunction from the SOFA score, but only a trend towards earlier improvement in organ function, with no significant difference between the two groups, was found.

References

1. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomised, double-blind, single-center study. Crit Care Med. 1999, 27: 723-732.