Glucocorticoid administration in sepsis and septic shock: time for a paradigm change?

POINT OF VIEW

Glucocorticoid administration in sepsis and septic shock: time for a paradigm change?

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ABSTRACT

The use of corticosteroids in patients with septic shock remains controversial. Questions remain regarding the more appropriate dose, the optimal timing to initiate therapy, the selection of patients who will benefit most from the treatment and the exact mechanisms involved in their effectiveness. Recent studies have highlighted that, in critically ill patients, corticosteroid metabolism was reduced and associated with high circulating cortisol levels. Hence the required doses of hydrocortisone may be lower than the currently recommended doses in septic shock (i.e. 200 mg/day). However, altered expression and/or function of corticosteroid receptors may still suggest that higher hydrocortisone doses are necessary to overcome this so-called "steroid-resistance". In this article, we summarized these recent concepts and discussed how they could influence the administration of corticosteroids in such patients.
(Minerva Anestesiol 2014;80:1058-62)

Key words: Steroids - Shock, septic - Metabolism.

Glucocorticoids (GCs) can have important haemodynamic and immunomodulatory effects in patients with septic shock and an adequate cortisol response is important to optimize survival rates in these patients.[1, 2] Since the 1940s, many clinical trials have investigated the role of glucocorticoids (GCs) in septic shock.[3] Following controversial results with high-dose steroids in the 1980s,[4] the use of GCs in patients with sepsis decreased. Furthermore, other studies suggested that hydrocortisone (HC), which is the endogenous GC released by the adrenal gland, was associated with rapid reversal of shock and might be considered as the best choice of replacement in this setting (Table I).[5, 6] In 2002, Annane *et al.*[7] tested a 7-day GC treatment (combining "moderate" dose HC [50 mg q6h] with fludrocortisone [50 μg once daily]) against placebo in patients with septic shock refractory to vasopressor agents. The authors found that patients who did not respond adequately to a corticotropin test (*i.e.*, patients with relative adrenal insufficiency) had improved survival if they received GC treatment; this was not the case in corticotropin-test responders. This study was criticized because of the definition of shock used (*i.e.*, systolic blood pressure less than 90 mmHg for one hour despite fluid and vasopressors), the high mortality observed in the control group (63%) and the need for statistical adjustment to obtain significant differences between groups. In two following studies,[8, 9] small doses HC were associated with better shock reversal and reduced cytokine levels in patients with septic shock, but the small number of patients precluded any estimation of the effects of this therapy on outcome.

Hence, a multicenter, randomized, double-blind trial, the CORTICUS study,[10] was designed to confirm the findings in a large population of patients with septic shock. This study

Table I.—*Summary of the main studies evaluating the use of hydrocortisone (HC) in patients with septic shock.*

Study	N. of patients	Type of Study	GCs Daily Doses	Time to CSI initiation *	Main Outcome
Briegel [5]	40	RCT	HC 100 mg LD + 0.18 mg/kg/h	<72 hrs	ICU-day survival rate: 20% (GCs) vs. 30% (placebo)
Bollaert [6]	41	RCT	HC 300 mg	>48 hrs	28-day survival rate: 68% (GCs) vs. 37% (placebo)
Annane [7]	300	RCT	HC 200 mg + FC 50 mcg	<24 hrs	28-day survival rate: 53% (GCs) vs. 63% (placebo)
Oppert [8]	41	RCT	HC 100 mg LD + 0.18 mg/kg/h	<24 hrs	28-day survival rate: 39% (GCs) vs. 48% (placebo)
Mussack [9]	24	RCT	HC 100 mg LD + 0.18 mg/kg/h	<72 hrs	ICU-day survival rate: 25% (GCs) vs. 42% (placebo)
Sprung [10]	499	RCT	HC 200 mg	<72 hrs	28-day survival rate in patients without response to ACTH test: 39% (GCs) vs 36% (placebo)
Ferrer [11]	1878 (total of 2796)	Prospective observational multicenter study	HC 200 mg	<72 hrs	Adjusted hospital mortality if on GCs: OR 1.04 [95% CI: 0.85-1.28]; p = 0.688
Casserly [12]	8992 (total of 27836)	Post-hoc analysis of the SSC database	HC 200 mg	<24 hrs	Adjusted hospital mortality if on GCs OR 1.1 [95 % CI: 1.09-1.23]; p <0.001
Arabi [13]	75	RCT	HC 200 mg	<24 hrs	Adjusted 28-day mortality if on GCs RR 1.17 [95% CI: 0.92-1.49]; p = 0.19
Miller [14]	4329	Prospective observational multicenter study	HC 200 mg	<24 hrs	Survival rate over a period of 7 years: 22% (GCs) vs. 10% (no GCs)

N: number; GCs: glucocorticoids; HC: hydrocortisone; FC: fludrocortisone; RCT: randomized clinical trial; SSC: surviving sepsis campaign: ACTH: corticotropin hormon; OR: odds ratio; CI: confidence interval; RR: relative risk; LD: loading dose; ICU: intensive care unit.
*from shock onset

reported, as did the Annane study,[7] that the use of HC (50 mg q6h for 5 days) was associated with a shorter time to vasopressor weaning. However, GC administration was not associated with beneficial effects on survival in the overall population or in the subgroup of patients with relative adrenal insufficiency. The results of this study challenged the routinely use of GCs in patients with septic shock.

Recent data

Other recent studies have also failed to demonstrate effectiveness of steroid therapy in patients with septic shock. In a prospective observational study evaluating the effects on outcome of treatments recommended in current guidelines for sepsis management, early broad-spectrum antibiotics and drotrecogin alfa (DAA) were associated with lower in-hospital mortality, but not steroids.[11] Moreover, a *post-hoc* analysis of the Surviving Sepsis Campaign database demonstrated increased hospital mortality in septic patients treated with GCs, even after adjusting for baseline severity of illness.[12] In patients with cirrhosis and septic shock, Arabi *et al.*[13] showed that the administration of HC group had a significant reduction in vasopressor doses and higher rates of shock reversal; however it was not associated with a significant reduction in 28-day mortality (P=0.19) but with an increase in shock relapse and gastrointestinal bleeding. On the opposite, Miller *et al.*[14] reported that the compliance to several treatment bundles of septic shock, including GCs, contributed to significantly reduce the mortality from 21.7% to 9.7% over a 7-year period.

Although there are significant methodological differences between the various studies, which may, at least in part, explain the contrasting results, recent theories about cortisol metabolism and activity may also shed some light on this controversial issue. Boonen *et al.*[15] studied the balance between GC production and catabolism in 158 ICU patients, in order to ascertain whether reduced cortisol metabolism during critical

illness could contribute to sustain hypercortisolaemia and to enhance the negative feedback inhibition of corticotropin. These authors found that total and free circulating cortisol levels were significantly higher in ICU patients compared to healthy control subjects (cortisol production was 83% higher in critically ill patients, along with a 50% reduction in cortisol clearance and reduced corticotropin levels). These results were explained by suppressed expression and activity of the main cortisol metabolizing enzymes in liver and kidney. Despite some limitations (single-centre study, high variability in inter-individual responses), this recent trial suggested that reduced cortisol breakdown may be, in part, responsible for the increased circulating cortisol levels seen in these patients and administering even moderate-dose GCs may result in cortisol levels that are excessively high, even for patients with putative adrenal failure. According to these data, lower daily doses of HC (*e.g.*, 60-70 mg) should be tested in patients with septic shock.

An additional factor that may influence response to GCs is GC-resistance. In a recent study, Guerrero *et al.*[16] hypothesized that proinflammatory cytokines in septic patients could modulate the expression of GC receptors (GRs), which mediate the actions of GCs. The α- and β-isoforms are the most widely studied types of GR. GRα promote GC actions, whereas GRβ have a predominantly inhibitory effect. Greater GRβ expression, as already observed in other inflammatory conditions, may induce GC resistance. In fact, in this study, the expression of GRβ in mononuclear cells from nine patients with septic shock was significantly higher on admission than on discharge, and serum from these patients induced GC resistance in vitro, confirming the initial hypothesis. Although previous studies have already shown that administration of high-dose steroids in patients with septic shock increases morbidity and mortality,[4] Guerrero *et al.* suggested that higher GC doses may be needed to overcome GC-resistance in this setting. Hence, therapeutic strategies aimed at improving GR sensitivity to endogenous corticosteroids may be more appropriate; however, no clinical data are available to support such an intervention.

How to use GCs in septic shock?

Over the last few decades, we have moved from the use of large doses of GCs in patients with septic shock to moderate or so-called "stress" doses. Recent studies have, however, suggested limited impact of "stress" dose GC administration on patients' outcome,[10-12] encouraging us to rethink this topic. We believe that, at the current time, three key issues should be considered. First, at the "moderate" doses that have been studied, GCs have no global beneficial effects on outcomes and use should currently be restricted to those patients with persistent requirement for high-dose vasopressors to facilitate shock reversal as recommended by the Surviving Sepsis Campaign guidelines.[17] Before the initiation of GCs treatment, hemodynamic optimization should be obtained with an adequate fluid therapy and the administration of adrenergic agents, if needed. Alternative vasopressors, such as vasopressin (added to or substituted for norepinephrine), could also be considered, probably as an early therapeutic option.[18] It is only when vasopressor requirement remains high that the identification of those patients that may more benefit from GCs therapy should be started in this setting.

Thus, as hypercortisolemia is related, in part, to reduced GCs catabolism, the second issue concerns the doses of GCs to administer, since smaller doses than those proposed by Annane et al. may be preferable. Indeed, this dose of 200 mg HC per day suggested by the Surviving Sepsis Campaign Guidelines [17] is at least six times higher than the normal daily cortisol production in healthy humans (25-30 mg/day);[15] this can result in very high GCs circulating levels, with an increased risk of adverse effects, such as critical illness weakness, bleeding and infections.

Third issue, additional therapeutic interventions that could increase GR sensitivity or alter the expression of GR subtypes in order to reduce GCs resistance in this setting should be a focus for future research. Baker *et al.* showed that single-nucleotide polymorphisms of the GR could enhance or decrease response to GCs.[19] These data emphasize the role of individualized doses, although it remains challenging to identify the specific clinical biomarkers of GRs activation to guide steroid therapy.

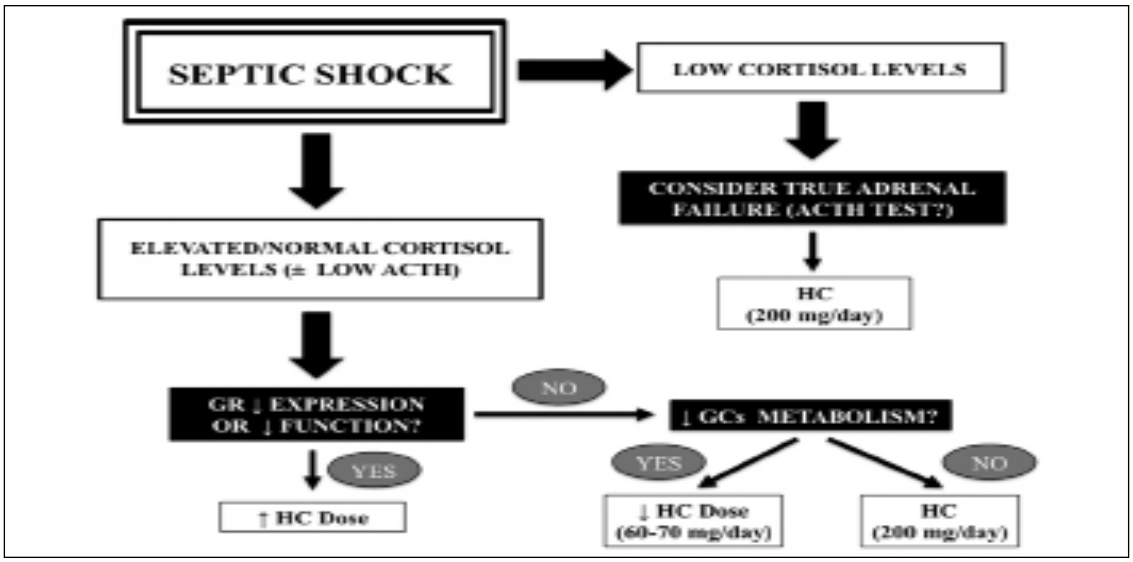

Figure 1.—Potential adaption of daily hydrocortisone (HC) doses according to the initial cortisol levels, the function of the glucocorticoids receptor (GR) or their metabolism.

Moreover, GR expression could be progressively decreased in sepsis and GCs may have a decreased ability to translocate into the cellular nucleus.[20] Also, the sensitivity of GR to circulating GCs may depend on the receptor dimerization, which is inhibited by pro-inflammatory mediators.[21]

How to make these two issues (*i.e.* the need for lower than standard HC doses and the GC-resistance) coexist in the daily management of septic shock patients? We clearly need some tools to better quantify the intensity of metabolic disturbance of GCs during sepsis as well as the degree of receptor activity and resistance in such patients' population. Unfortunately, the measurement of total and/or free cortisol concentrations is not very helpful in this setting. Nevertheless, a lower total and cytoplasmic receptor levels, as it has been shown in critically ill children on peripheral blood mononuclear cells, may be used to estimate the GR-mediated response to exogenous GCs therapy during sepsis. In case of reduced GR expression, "stress" (*i.e.* 200 mg/day of HC) or even higher GCs doses should be initiated while lower regimens could be considered in case of normal GR production and reduced GCs metabolism (Figure 1). Importantly, measurement of GR expression is not predictive of receptor functionality and an accurate cut-off to define GR expression as "reduced" or "normal" remains to be defined. A more accurate method to evaluate GR activity could be the genomic response to GC administration. In pediatric septic shock, GC induced a repression of genes corresponding to adaptive immunity;[23] the analysis of gene expression related to GR could potentially help when considering the benefit to risk ratio of GCs therapy for septic shock. Finally, whether GR expression and GCs metabolism change during the time-course of sepsis may also explain why steroid treatment may be beneficial only in some disease stages, as the early phase when the pro-inflammatory mediators are responsible for most of cellular injury, and become ineffective or even deleterious in others, such as the late phase where innate immune response begins to recover.

An ongoing study, the ADRENAL (ADjunctive corticosteroid tREatment iN critically ilL patients with septic shock) Trial,[22] evaluating the effects of moderate doses of GCs in septic shock, should provide additional data on the use of this therapy in this setting. Future studies should focus on the concept of individual assessment of GCs metabolism and GR function in order to help clinicians to adjust GCs therapy in patients with septic shock.

Key messages

— The use of "stress" doses (*i.e.* 200 mg/day) of HC in patients with septic shock remains controversial.

— Recent studies have highlighted a reduction in corticosteroids metabolism in patients with septic shock, which would potentially need a reduction of standard HC regimens.

— Altered expression and/or function of corticosteroid receptors may suggest the increase of HC doses to avoid steroid resistance.

— Future studies should focus on the identification of reliable tools to better define the degree of altered adrenal function and/or GR function during critical illness to optimize HC administration in this setting.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on March 12, 2014 – Accepted for publication on June 25, 2014.

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Epub ahead of print on June 27, 2014.