Corticosteroids in Sepsis: A New Concept for an Old Drug

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Abstract

Sepsis is an inflammatory syndrome caused by infection. Consequently, anti-inflammatory therapy in sepsis has been a subject of extensive research, and corticosteroids have long been used to treat severe infections. However, studies conducted in the 1980s failed to demonstrate any beneficial effects of high dose, short-term steroid therapy in sepsis and this therapy was therefore abandoned in the last decade. Recently, a new concept has emerged with more promising results – low dose, long-term hydrocortisone therapy – and this approach is now being evaluated in the treatment of septic shock. It is supported by the observation that many sepsis patients have relative adrenal insufficiency. Moreover, the anti-inflammatory effects of steroids and their ability to improve reactivity to catecholamines further contribute to their effects in sepsis. Large randomized clinical trials will be required to determine the exact role of corticosteroids in septic shock.

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Sepsis is an infection-induced syndrome defined as the presence of two or more of the following features of systemic inflammation: hyperthermia or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or supranormal minute ventilation [1]. Systemic inflammatory response syndrome is the result of several insults whose purpose is to limit and reverse the injury. The outcome and intensity of the inflammatory response is determined by the severity of the injury and the balance between inflammatory and compensatory anti-inflammatory responses [2]. The mortality rate among patients with septic shock is approximately 40% [2]. Sepsis, septic shock, and adverse sequelae of the systemic inflammatory response to infection currently constitute the 13th most common causes of death in the United States and are among the most common causes of death in the non-coronary intensive care unit [3]. It is well known that stress, including severe illness, trauma, anesthesia, and surgery, is accompanied by activation of the hypothalamic-pituitary-adrenal axis, resulting in increased levels of both gluco- and mineralocorticosteroids [4].

It was initially believed that early anti-inflammatory therapies could affect the course and outcome of severe sepsis and septic shock. Corticosteroids were among the first anti-inflammatory, immunomodulating drugs tested in septic patients. However, in complex situations such as sepsis or septic shock, multiple cellular activation processes are involved and many humoral cascades are triggered, so that merely blocking a single component may be insufficient to arrest the inflammatory process. Indeed, studies using high dose corticosteroids failed to demonstrate beneficial effects; moreover, some of these trials reflected an increased mortality in septic patients treated with corticosteroids [5]. Recently, a new concept emerged using low dose long-term corticosteroids for sepsis-induced adrenal insufficiency and catecholamine-dependent sepsis. Results of small, randomized clinical trials are promising, suggesting a new role for corticosteroids in sepsis [6]. Large randomized controlled trials are now underway to determine the exact role of this renewed use of corticosteroids.

Pathophysiology

Sepsis

Sepsis and systemic inflammatory response syndrome are associated with an exacerbated production of cytokines. In fact, systemic inflammatory response syndrome is considered a syndrome of hypercytokinemia [4]. An excessive or poorly regulated immune response may harm the host through a maladaptive release of endogenously generated inflammatory compounds [7]. The complexity of immunologic defenses makes the development of pharmacologic interventions difficult [Figure 1]. A key arm in the cascade is cytokines – host-produced, pleomorphic immunoregulatory peptides. Cytokine biology is presently poorly understood

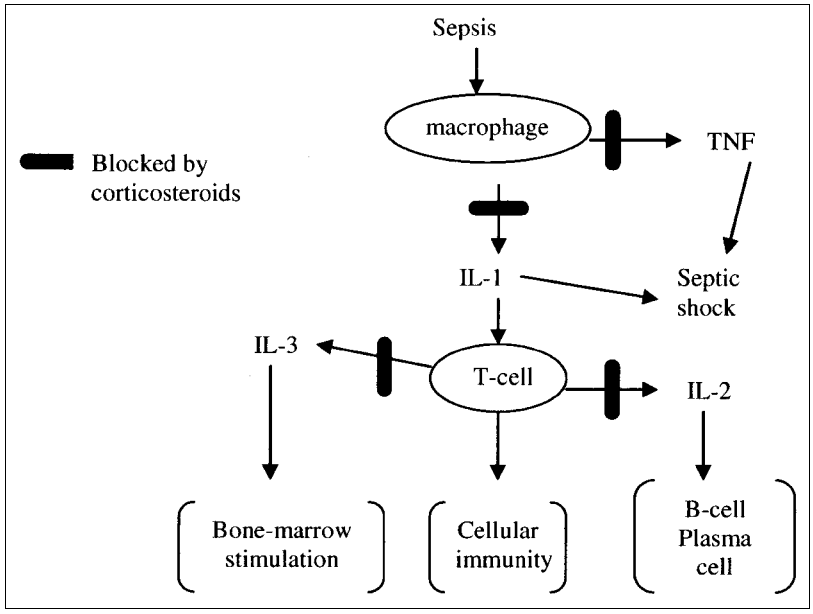

Figure 1. Glucocorticoid effects on immune/inflammatory response

Table 1. Anti-inflammatory effect of corticosteroids

Effects through lipocortins	Effects on interleukins	Effects on neutrophils	Other effects
Enables the PMNs to respond to stimulus.	Inhibition of synthesis of IL-1.	Stabilizes neutrophilic lysosomes.	Prevents activation of the complement cascade.
Inhibits phospholipase A2 and prevents prostaglandin generation.	Inhibition of IL-6.	Inhibits release of lysosomal enzymes.	Inhibits exogenous nitric oxide synthase.
Changes in membrane bound Ca^{+2}.	Reduces half-life of IL-3 mRNA.	Inhibits chemotaxis.	Decreases platelet-activating factor during endotoxin challenge.
Inhibits the ability of neutrophils to release active oxygen metabolites	Down-regulates cytokines and growth factors.	Disrupts the normal amplification of an inflammatory response.	
	Prevents TNF and IL-1 release from mononuclear cells.	Prevents hyperaggregation and adhesion of leukocytes induced by endotoxin.	

PMNs = polymorphonuclear cells

and simple anti-cytokine strategies have failed to improve survival of critically ill patients, probably reflecting the complexity, heterogeneity and at times irreversibility of this syndrome [8].

Corticosteroids

The exact mechanisms whereby corticosteroids or mineralocorticoids exert their effects on tissue function are unknown. However, in therapies other than adrenal replacements, the anti-inflammatory and/or immunosuppressive actions of the glucocorticoids are the principal desired qualities. Table 1 summarizes the anti-inflammatory properties of glucocorticoids [9].

Because of their anti-inflammatory effects, the glucocorticoids were previously thought to improve the course and reduce the mortality of septic shock. They were reported to be able to perform a number of beneficial functions, such as disaggregating clumps of granulocytes, stabilizing lysosomal enzymes and capillary membranes, minimizing capillary permeability, improving oxygenation by altering ventilation/perfusion mismatches, increasing cardiac contractility, antagonizing complement and reducing complement-mediated granulocytic aggregation, diminishing coagulopathy, antagonizing endotoxin effects, decreasing local inflammatory responses and release of mediators [10], altering the migratory patterns of inflammatory cells, reducing toxic oxygen radical release, and vasoconstricting the capillary bed either directly or indirectly through the potentiation of the adrenergic system. Most of these effects are probably mediated through the effects of glucocorticoids on cellular lipocortins, which interfere with the release and metabolism of arachidonic acid [9].

The first study suggesting the therapeutic use of corticosteroids (hydrocortisone in physiologic doses) in patients with bacteremia or generalized severe infection was published in 1951 [11]. In 1976, a prospective study of septic patients by Schumer [12] indicated that methylprednisolone (30 mg/kg) or dexamethasone (3 mg/kg) given once or twice in 24 hours reduced the mortality from 38.4% to 10.5%. Later, in 1984, Sprung et al. [5] also conducted a prospective controlled study of steroids in sepsis and found that treated patients were more likely to have their shock reversed, but the overall survival rate was similar in both groups [12]. The authors suggested an increased survival rate with early high dose steroid treatment [5,12]. Several other experimental animal studies further suggested that early glucocorticoid therapy could blunt the effects of sepsis, improve survival, reduce pulmonary hypertension, and decrease high permeability pulmonary edema associated with endotoxin infusion. These animal studies suggested that early administration of glucocorticoids could improve survival [9].

In 1984, Hoffman et al. [13] showed a reduction in mortality from severe typhoid fever by high dose dexamethasone. In 1990, Gagnon and co-workers [14] conducted a double-blind, placebo-controlled trial, showing a beneficial effect of corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in AIDS. In another trial, beneficial effects of early dexamethasone administration were demonstrated in infants and children with bacterial meningitis [15].

In 1995, two large meta-analyses were published reviewing the data pertaining to the use of corticosteroids in sepsis. Both papers concluded that there is no overall beneficial effect of corticosteroids in patients with septic shock and that their use may be harmful [12]. Randomized trials showed that a short course of a large dose of anti-inflammatory steroids is ineffective and potentially harmful in patients with severe sepsis [5,12]. Table 2 summarizes these two large meta-analyses and their results. It was concluded that a short course of high dose corticosteroids should not be administered in severe sepsis [6]. Consequently, high dose corticosteroid therapy for the treatment of severe sepsis was abandoned.

Low dose corticosteroids – a novel concept

Recently, several studies reported beneficial effects of lower doses of hydrocortisone in septic shock. These reports of the use of steroids in supraphysiologic doses in patients with sustained circulatory instability have re-ignited the debate [6,16,17]. Two small, double-blinded, randomized studies were published, demonstrating that prolonged treatment with low dose hydrocortisone (100 mg i.v. three times daily for 5 days) in septic shock reduced the time to shock reversal, the systemic vascular resistance, expedited weaning from vasopressor therapy, and most importantly, reduced mortality [18,19]. In the context of renewed interest in corticosteroids as therapy for septic shock, Annane and colleagues [20] showed that adrenocorticotropic hormone stimulation test could be used as a good prognostic value in septic shock and could be helpful in identifying patients with septic shock at high risk for death.

Table 2. Summary from the meta-analyses by Lefering et al. [12] and Cronin et al. [5]. (Total number of patients = 1,297)

Author	Year	No. of patients	Drug	Dose	Duration	Risk ratio (95% confidence interval)
Luce et al.	1988	75	MP	30 mg/kg (x4)	24 hr	1.07 (0.72–1.6)
Veterans administration	1987	223	MP	30 mg/kg followed by 5 mg/kg	9 hr	0.95 (0.57–1.8)
Bone et al.	1987	381	MP	30 mg/kg	24 hr	1.35 (0.98–1.84)
Sprung et al.	1984	59	MP	30 mg/kg	1 or 2 doses	1.11 (0.74–1.67)
Lucas et al.	1984	48	DM	6 mg/kg	48 hr	1.09 (0.36–3.27)
Thompson et al.	1976	60	MP	30 mg/kg	Up to 4 hr in 24 hr	1.01 (0.77–1.31)
Schumer	1976	172	MP	30 mg/kg	1 or 2 doses	0.3 (0.13–0.72)
Klastersky et al.	1971	85	BM	1 mg/kg	72 hr	0.97 (0.65–1.45)
Cooperative study group	1963	194	HC	300 mg followed by 50 mg/day	6 days	1.72 (1.23–2.41)

MP = methylprednisolone, DM = dexamethasone, BM = betamethasone, HC = hydrocortisone.

The results of a recently completed multicenter, placebo-controlled, randomized, double-blind study are still to be published. This study included 299 episodes of catecholamine-dependent septic shock (149 with placebo, 150 with treatment). Patients were randomized to receive either 50 mg of intravenous hydrocortisone 4 times daily or 50 g of fluorocortisone orally for 7 days starting 8 hours following the onset of shock or placebo. This study demonstrated that treatment with low dose steroids resulted in a 30% decrease in the risk of death in septic shock patients ($P < 0.05$) [21,22].

There are two proposed mechanisms for the beneficial effect of corticosteroids in sepsis: relative adrenal insufficiency, and anti-inflammatory effect.

Relative adrenal-insufficiency and catecholamine-dependent septic shock

The HPA axis has an important role in the stress response, i.e., physiologic response to stresses such as infections, hypotension and surgery [23]. The activity of the HPA axis is influenced by free unbound or active cortisol fraction to keep glucocorticoid activity within the normal range. Decreased plasma cortisol levels lead to an increase in ACTH and corticotropin-releasing hormone secretion and, subsequently, cortisol secretion [24]. Stress can override the normal regulatory influences and diurnal rhythm and lead to sustained increases in ACTH secretion and plasma cortisol concentrations [25]. The stress response is probably mediated primarily by the central nervous system through the release of CRH, although other hormones may also be involved. Several cytokines, including platelet-activating factor, gamma-interferon, interleukins 1, 2 and 6, and tumor necrosis factor, can activate the HPA axis [26].

Recent demonstrations of altered HPA axis response in sepsis have led to a reappraisal of the use of steroids in septic shock [20]. Systemic inflammatory states such as sepsis can be associated with reversible and relative adrenal insufficiency due to HPA axis suppression by several mechanisms [27]. This syndrome of relative adrenal insufficiency is defined as inappropriately low serum cortisol concentrations, an impaired serum cortisol response to corticotropin, or a rapid clinical response to exogenous corticosteroids, diminishing or eliminating the requirement for vasopressive agents [Figure 2] [28]. Relative adrenal insufficiency may be due to HPA axis suppression by cytokines and other inflammatory mediators [29]. Immune products such as TNFα and corticostatin may inhibit adrenal function and cortisol production. Other circulating substances may also be responsible for inhibition of adrenal function. Corticostatin, a peptide found in immune cells, has been shown to impair adrenal cortical function by competing with ACTH by binding to its receptor. In addition, the number and affinity of cellular glucocorticoid receptors are decreased, which in turn decreases cortisol action at the cellular level [30]. A peripheral glucocorticoid resistance syndrome may occur in patients with septic shock, possibly contributing to excessive immune-mediated inflammation as found in rheumatoid arthritis, corticosteroid-resistant asthma, AIDS, and chronic degenerative osteoarthritis [31].

ACTH stimulation test is considered a simple and safe screening test to confirm suspected adrenal insufficiency: adrenal function being defined by plasma cortisol level before, and 30 and 60 minutes after injection of corticotropin [Figure 2]. Normal plasma cortisol response to CRH is defined as basal or peak plasma cortisol concentration > 550 nmol/L (20 μg/dl). In patients with severe secondary adrenal insufficiency, plasma cortisol increases little or not at all after administration of corticotropin. The recognition of adrenal insufficiency and interventions to improve adrenal responsiveness may contribute to improving the outcome during late septic shock [Figure 2] [20]. However, controversy still exists regarding the diagnosis and significance of relative adrenal insufficiency. Therefore, adrenal insufficiency in severe sepsis should be considered as a functional rather than a biochemical diagnosis.

HPA = hypothalamic-pituitary-adrenal
ACTH = adrenocorticotropic hormone
CRH = corticotropin-releasing hormone
TNF = tumor necrosis factor

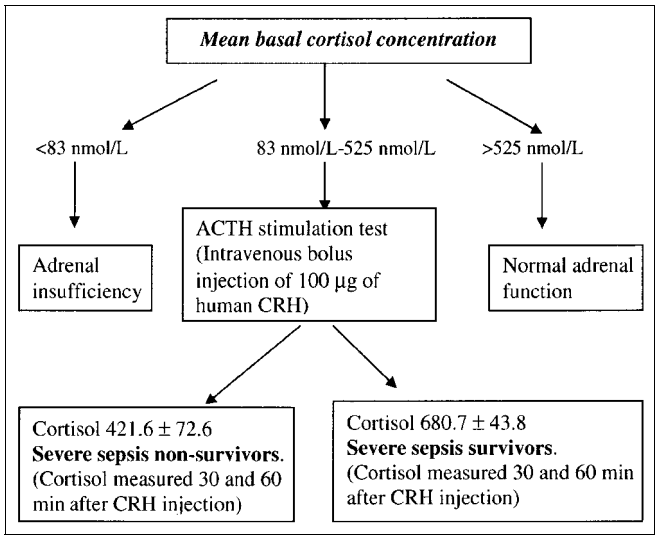

Figure 2. ACTH stimulation test in severe sepsis survivors vs. non-survivors

Septic shock is characterized by decreased responsiveness to catecholamines. Randomized trials in catecholamine-dependent septic shock patients strongly suggest that replacement therapy with hydrocortisone may alleviate the symptoms of systemic inflammatory response, reduce the duration of shock, and favorably affect survival [32,33]. For example, in patients with septic shock, the Emax of phenylephrine is decreased, whereas its ED50 is not modified, and a physiologic dose of hydrocortisone tends to normalize the relationship. Corticosteroids may restore catecholamine receptor sensitivity, which has been shown to be desensitized or down-regulated during prolonged septic shock [34]. Studies in dogs and cats have demonstrated that the vasoconstrictor response to epinephrine is enhanced by cortisol and aldosterone. In Wistar rats, administration of the corticosteroid antagonist RU 486 induced a 20 mmHg drop in mean arterial pressure with unchanged cardiac output, depicting the role of cortisol in maintaining systemic vascular resistance [35,36]. Despite our increased knowledge, the precise mechanisms whereby corticosteroids regulate cardiovascular homeostasis remain incompletely understood [37].

Anti-inflammatory effect: nuclear factor κB

Corticosteroids may attenuate the systemic inflammatory response syndrome and restore the balance between inflammation and anti-inflammation that is disrupted during sepsis. This effect is mediated by the influence of steroids on the transcription of genes that code for inflammatory proteins, such as cytokines, enzymes and adhesion molecules. Nuclear factor κB is the primary transcription factor affected by steroids [38]. NF-κB is a nuclear transcription factor that plays a pivotal role in the production of pro-inflammatory mediators. Its activity is regulated by control of its nuclear localization. NF-κB expression has been shown to be elevated in patients with sepsis, and a persistently increased expression is related to poor outcome. Upon cell stimulation, the inhibitory I-κB protein is released, allowing translocation of NF-κB to the nucleus. Binding NF-κB to its DNA binding site results in expression of the pro-inflammatory mediator messenger RNA [39].

Recent data suggest that the mechanism responsible for the clinical effects of supraphysiologic doses of corticosteroids in late septic shock is directly related to the inhibition of nuclear factor κB in peripheral blood mononuclear cells. Moreover, corticosteroids induce the expression of I-κB, an inhibitor of NF-κB [40].

NF = nuclear factor

Summary

High anti-inflammatory doses of corticosteroids have failed in the treatment of septic shock. A promising new concept is emerging – low dose corticosteroids. The proposed mechanism of low dose glucocorticoid therapy is not fully understood. Neither the ACTH stimulation test, nor the amount of NF-κB can be used to guide therapy. The exact patient population that will benefit the most from this treatment is yet to be determined, and larger controlled studies are still awaited. Based on current knowledge no firm recommendation can yet be made. However, low dose corticosteroids should be considered in every patient with vasopressor-dependent septic shock, while carefully weighing the risks and the benefits of this promising concept.

Addendum

While this paper was in the proof stage a new study by Annane and colleagues was published (Effect of treatment with low doses of hydrocortisone and fluorocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862–71). In this trial 300 adult patients with septic shock were randomly assigned to receive either low doses of hydrocortisone and fludrocortisone (n=151) or matching placebos (n=149) for 7 days. A significant reduction in risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse effects was observed. This study provides additional support to the beneficial role of low dose steroids in septic shock.

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