Steroid Therapy During Septic Shock: A Second Birth?

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LEADING ARTICLE

Corticosteroids have been used for years in the therapy of severe infections. However, studies conducted in the 1980s failed to show any beneficial effect of high doses used for very short-term therapy. More encouragingly, recent data show far more positive results, with a reduction in mortality, principally in severe septic shock patients who did not respond to a corticotropin test. This effect is supported by the discovery that most patients with severe septic shock have a 'functional' or 'relative' adrenal insufficiency. Thus, corticosteroids could have several positive effects during septic shock: in addition to supplementing adrenal insufficiency, they have a well-known anti-inflammatory effect, and can increase the reactivity of receptors to catecholamines. Further trial results are awaited that will enable the physician to make a more informed clinical choice.

Use of steroids in the past

Corticosteroids have been used for decades in the treatment of serious infections, despite continuing controversy regarding their efficacy. Numerous animal studies performed during experimental septic (endotoxic) shock or acute lung injury showed a highly significant reduction in both the intensity of shock, acute respiratory failure and mortality, provided the drug was used early enough (ideally before the insult) [1,2]. They were used in the past at very high doses (30 mg/kg per dose for a maximum of 24–48 h). The ability of these high doses to reduce complement activation and to inhibit leukocyte aggregability and adherence to endothelium was a logical rationale for their efficacy [3]. In humans, promising initial results were published [4]. However, in the early 1980s, two well-designed, large prospective, multicenter, randomized, double-blind studies did not demonstrate any ability of steroids to decrease mortality [5,6]. Conversely, some studies reported positive trends when looking at subgroups of infections, in particular those due to Gram-negative rods [5–7]. It has to be emphasized that, although these studies involved 300–400 patients, this is far smaller than current trials.

Two recent meta-analyses confirmed that corticosteroids, at the dose of 30 mg/kg (one or two doses), were ineffective [7], or even harmful [8]. The design and the results of the nine randomized studies are detailed in Tables 1 and 2. Pooling the results from those patients with Gram-negative infections, as performed in the meta-analysis by Lefering and Neugebauer [7], yields a rate difference of –5.6 % (95% confidence interval [CI] –21.4 to 10.1) in favor of steroids, based on 413 patients. Patients with Gram-positive infections (n=306) experienced an overall effect of +1.8 % (95% CI –15.8 to 18.6). Most people stopped using steroids when these large trials were published.

More recent trials

Several studies, however, have sustained some interest in the use of corticosteroids [9,10], for example, showing reduced mortality during meningitis in children [10]. Two large, double-blind, case-control studies demonstrated that prolonged treatment (10–15 days) of relatively low doses of steroids (120–240 mg hydrocortisone)

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Table 1. Design of the nine randomized studies used in the meta-analysis from Cronin et al. [8].

Authors	Year	Number of patients	Type of study	Product	Dose	Duration	Endpoints
Cooperative study group [21]	1963	194	Open	H	300 mg, then 50 mg/day	6 days	Mortality Complications
Klastersky et al. [22]	1971	85	Open	B	1 mg/kg	3 days	Mortality (20-day) Complications
Schumer [4]	1976	172	Double-blind	M	30 mg/kg	1 or 2 doses	Mortality (28-day) Complications
Thompson et al. [23]	1976	60	Double-blind	M	30 mg/kg	Max. 6 doses in 24 h	Mortality Complications
Lucas et al. [24]	1984	48	Open	D	2 mg/kg	2 days	Mortality (14-day) Complications
Sprung et al. [25]	1984	59	Open	M	30 mg/kg	1 dose (or 2)	Hospital Mortality Complications
Bone et al. [5]	1987	381	Double-blind	M	30 mg/kg	1 day	Mortality (14-day) Complications
Veteran's Administration [6]	1987	223	Double-blind	M	30 mg/kg	9 days	Mortality (14-day) Complications
Luce et al. [26]	1988	75	Double-blind	M	30 mg/kg x 4	1 day	Hospital mortality Acute respiratory distress syndrome complications

B: betamethasone; D: dexamethasone; H: hydrocortisone; M: methylprednisolone.

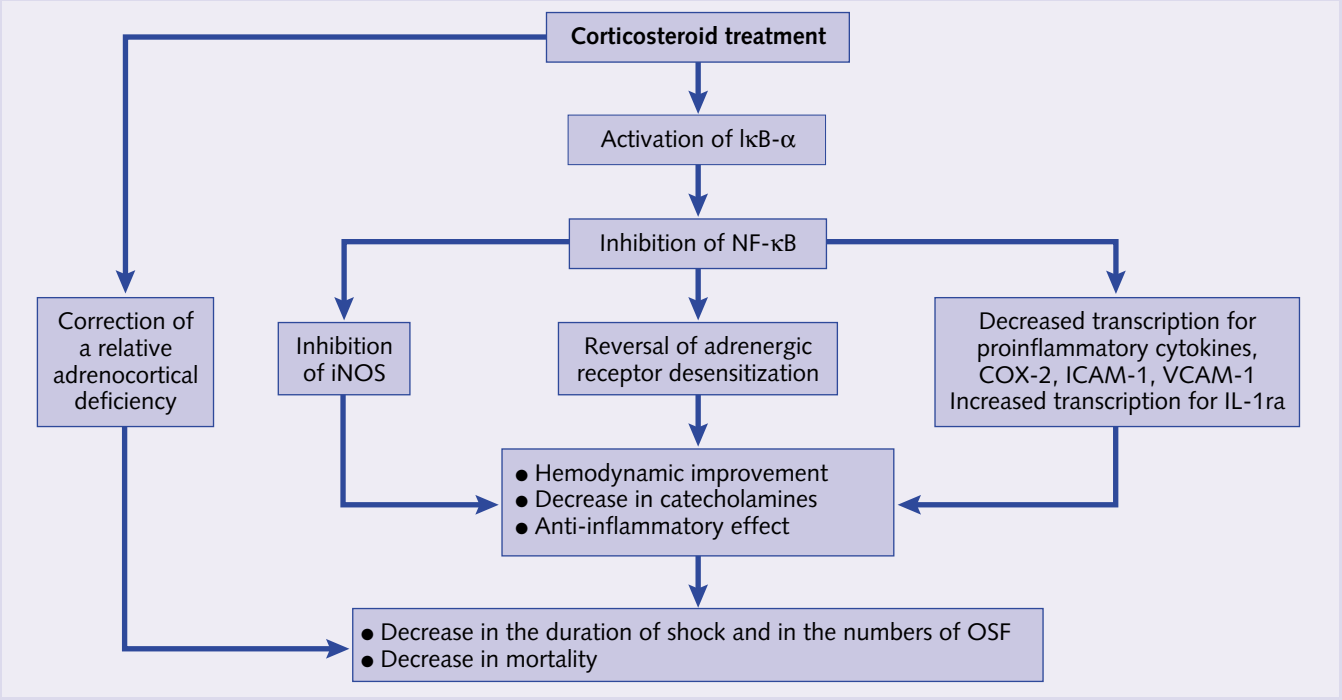
Table 2. Results of the nine randomized studies used in the meta-analysis from Cronin et al. [8].

Study	Year	Number of patients	Risk ratio	95% Confidence interval
Cooperative study group [21]	1963	194	1.72	1.23–2.41
Klastersky et al. [22]	1971	85	0.97	0.65–1.45
Schumer [4]	1976	172	0.30	0.13–0.72
Thompson [23]	1976	60	1.01	0.77–1.31
Lucas et al. [24]	1984	48	1.09	0.36–3.27
Sprung et al. [25]	1984	59	1.11	0.74–1.67
Bone et al. [5]	1987	381	1.35	0.98–1.84
Veteran's Administration [6]	1987	223	0.95	0.57–1.58
Luce et al. [26]	1988	75	1.07	0.72–1.60

dramatically reduced mortality during severe *Pneumocystis carinii* pneumonia in AIDS patients [11,12]. After a long period of negative trials in the therapy of sepsis, two small, randomized, double-blind studies of steroids in patients with severe and refractory septic shock recently demonstrated positive results [13,14]. Corticosteroids were used at small doses (100 mg hydrocortisone three times a day in the first study [13] and 100 mg, followed by a continuous infusion of 0.18 mg/kg/h, in the second [14]). In both studies, treatment was given for longer periods of time than in the past: 5 days in the first study [13] and 5–10 days in the second, with dose tapering according to hemodynamic status and need for vasopressor use. Both studies showed consistent results, with a significant reversal of shock and organ failures, and a trend towards reduced mortality. A recent French multicenter randomized, controlled, double-blind study confirmed these initial positive results [15]. This study enrolled 299 patients with severe septic shock requiring the use of vasopressor agents. Upon trial entry, each patient was given a dynamic test with adrenocorticotropin (ACTH) to stratify the population into 'responders' or 'non-responders' to ACTH. Treated patients then received 50 mg of hydrocortisone every 5 h intravenously, and 50 mg of fluorocortisone enterally for 5 days.

Mortality was significantly reduced in the overall population (OR=0.712; 95% CI 0.525–0.965) and in the

Figure 1. Potential beneficial effects of corticosteroids during severe sepsis and septic shock.



COX: cyclooxygenase; IκB-α: inhibitor of NF-κB; ICAM: intercellular adhesion molecule; IL-1ra: interleukin-1 receptor antagonist; iNOS: inducible nitric oxide synthase; NF: nuclear factor; OSF: organ system failure; VCAM: vascular cell adhesion molecule. Adapted from [24].

subset of non-responders (OR=0.670; 95% CI 0.474–0.946). Although the trend was similar, the difference was not significant in the subset (n=70) of responders (OR=0.695; 95% CI 0.359–1.37). The incidence of side effects, in particular nosocomial infections, was similar in both groups.

Possible mechanisms of action

Several reasons may explain the recently reported positive effects of corticosteroids during sepsis [16] (Fig. 1). These include the treatment of a 'relative' adrenal insufficiency [17], and the increase in adrenergic receptivity [18,19], in addition to the anti-inflammatory effect. In particular, corticosteroids are known to induce the production of IκB-α, the inhibitor of nuclear factor-κB, a potent inflammatory signaling protein [17], and to reduce the production of type-2 cyclooxygenase (COX-2). A dose with a lower immunosuppressive effect and a more prolonged duration of therapy than in the initial studies could also explain, at least in part, the success obtained with steroids in these recent trials.

Conclusion

Recent data support the efficacy of low-dose steroids administered for a period of 5–10 days in the treatment of septic shock. Grade C in the evidence-based scale was, therefore, proposed before communication of the French study results in the guidelines of the International Sepsis Forum [20]. It is the belief of some experts that it should be possible to use steroids in septic shock, and perhaps in severe sepsis. The publication of the French study results should add consistency to this approach in the context of septic shock. However, waiting for a confirmatory study in the context of severe sepsis remains mandatory before making any solid clinical recommendation [20]. It is also important to emphasize that any potential nidus for infection clearly needs to be identified, evidenced, and treated as required, before starting any steroid treatment.

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