Crit Care & Shock (2004) 7: 129 - 133

Steroids in sepsis

Jose Chacko

Abstract

There has been considerable interest in the use of steroids in sepsis and septic shock from the 1970s. Early clinical trials with short term, high dose steroids showed either no benefit or increased mortality. Current evidence suggests that relative adrenal insufficiency is common in sepsis. This has led to renewed interest in the use of low, physiological doses of corticosteroids in septic shock. Small randomized controlled trials have shown earlier reversal of shock, reduced organ failures and a trend towards reduced mortality. One large trial has shown mortality reduction in a sub group of patients with documented adrenal insufficiency. It would seem appropriate to consider administration of low dose steroids to patients in septic shock who do not respond adequately to initial resuscitative measures and vasopressors.

Keywords: sepsis, corticosteroids, adrenal insufficiency, randomized controlled trials

Introduction

Sepsis is the systemic inflammatory response to the presence of documented infection [1]. The systemic inflammatory response syndrome (SIRS) is meant to limit and reverse the injury. The outcome and intensity of the inflammatory process is determined by the severity of the injury and the balance between inflammatory and compensatory anti-inflammatory responses [2]. The mortality rate in septic shock is approximately 40% [2]. Since septic shock carries with it substantial mortality, morbidity and economic burden, there is continued interest in novel therapies or modified applications of existing drugs to improve outcomes. Ever since the 1950 s, there has been considerable debate in the use of corticosteroids to improve outcomes in septic shock.

Pathophysiology of sepsis

SIRS is characterized by hypercytokinemia [3]. An excessive, uncontrolled immune response may harm the host through a maladaptive release of endogenously generated inflammatory compounds [4]. Cytokine biology is poorly understood and simple anti-cytokine strategies have failed to improve survival in critically ill patients, probably reflecting the complex heterogeneity and at times irreversibility of this syndrome [5]. In a syndrome of such complexity, multiple cellular activation processes are involved and many humoral cascades are triggered, so that merely blocking a single component would likely be inadequate to attenuate the inflammatory process. The results of a recent large multi centre study on the use of anti tumor necrosis factor antibody that failed to show a significant survival benefit in severe sepsis corroborates this [6].

Corticosteroids

Corticosteroids are used in many conditions characterized by excessive inflammatory response such as asthma, collagen vascular disorders, vasculitis, sarcoidosis, etc [7]. Septic shock evokes an even more profound inflammatory response characterized by persistent hypotension despite adequate fluid resuscitation, or the need for vasoactive drugs to support blood pressure coupled with evidence of reduced perfusion such as mental status changes, lactic acidosis, or decreased urine output [1]. Corticosteroids have been reported to be of value in these inflammatory states working through several mecha-

Address requests for reprints to:
Jose Chacko, MD, EDIC,Consultant, Critical Care, Manipal Hospital, Bangalore, India 560034
Tel: + 91 80 25211199. Fax: + 91 80 25287741.
E-mail: josechacko@medscape.com

nisms (**Table 1**). They disaggregate clumps of granulocytes, stabilize lysosomal enzymes and capillary membranes thereby minimizing capillary permeability, improve oxygenation through better ventilation/perfusion matching, improve cardiac contractility, antagonize complement and reduce complement-mediated granulocyte aggregation, diminish coagulopathy, antagonize endotoxin effects, decrease local inflammatory responses and release of mediators [8], alter the migratory patterns of inflammatory cells, reduce toxic oxygen radical release and constrict the capillary bed either directly or indirectly through the potentiation of the adrenergic system. These effects are probably mediated through the effects of glucocorticoids on cellular lipocortins, which interfere with the release and metabolism of arachidonic acid [9].

250 ±g of tetracosactrin carried the highest mortality [17]. If one looks at relative adrenal insufficiency in terms of non responders to ACTH (≤ 9 g/dl), then the mortality in that group was 72%, whereas in those who did respond to ACTH the mortality was 32% ˘ more than double. How common is relative adrenal insufficiency? In the study the abovementioned study, it was 54%, but in some recent data there are suggestions that between two-thirds and three-quarters of patients with septic shock may have relative adrenal insufficiency. In a study on nine patients with septic shock, pressor response to noradrenaline was significantly lower in those with adrenocortical insufficiency as defined by a peak rise in cortisol of less than 9 ±g/dL. A single IV dose of 50 mg of hydrocortisone significantly improved the blood pressure in these patients.[18] Thus, septic shock may result in down-regulation of catecholamine receptor sensitivity, with

Table 1. Anti-inflammatory effects of corticosteroids

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

PMNs = Polymorphonuclear leukocytes

The integrity of the hypothalamic-pituitary-adrenal (HPA) axis is a major determinant of the host s response to stress [10,11]. During sepsis, the activation of the HPA axis is highlighted by increased corticotropin release from the pituitary gland [12], enhanced adrenal secretory activity, and high plasma cortisol levels [13,14]. A state of relative insufficiency of the HPA axis may occur in sepsis and septic shock. A past study has shown that in the presence of adrenal insufficiency, there is reduced survival from severe illness [15]. Many studies have shown that basal cortisol levels in septic patients may be higher than normal, and indeed, such high levels may be associated with increased mortality [16]. This paradoxical relationship between high levels and decreased effect could mean a decreased affinity of the glucocorticoid receptor. Annane et al. showed that patients with a baseline cortisol of > 32 ±g/dL and a maximum rise of < 9 ±g/dL to impaired response to pressors. Severe sepsis and septic shock may be associated with a greater degree of impairment. Steroids may help restore catecholamine receptor sensitivity characterized by an increase in systemic vascular resistance and improved blood pressures. This effect on the vascular tone is independent of the adrenocortical function. Furthermore, steroids have been shown to inhibit the expression of inducible nitric oxide synthetase in vascular endothelium and to decrease the levels of soluble phospholipase A2 to almost normal, thereby reducing levels of free arachidonic acid and vasodilating prostaglandins in septic patients [19].

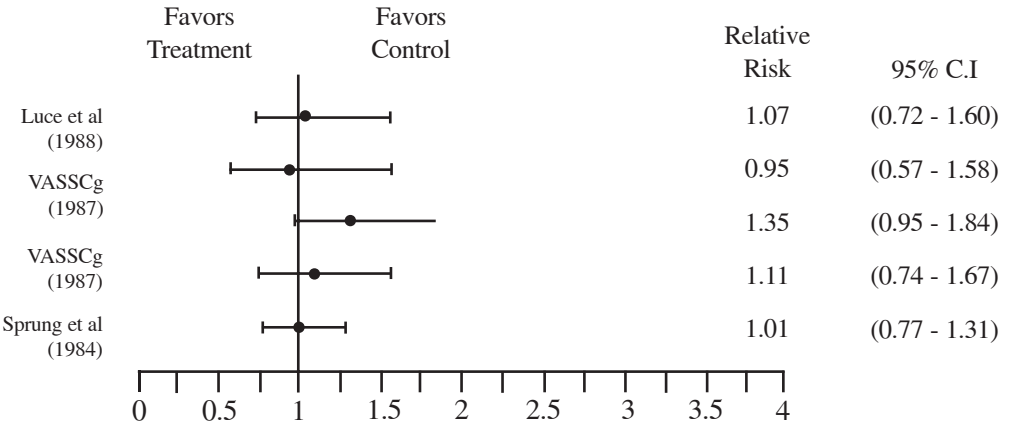
Steroids in sepsis – early trials

In the 70 s and the 80 s several studies were conducted using high ˘ dose, early administration of corticosteroids in patients with severe sepsis and septic shock. Schumer et al.

[20] in a prospective study of septic patients concluded 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%. Notwithstanding several criticisms, including the use of two different steroid preparations, lack of standardization of antibiotic and supportive treatment, lack of information concerning adjunctive therapeutic strategies and the unusually low mortality rate, many clinicians still continued to use this form of therapy in septic patients. The 1980 s saw several well ˘ designed trials. In an open ˘ label trial, Sprung et al. randomized 59 patients to receive methylprednisolone, 30 mg/ kg IV, dexamethasone 6mg/kg IV, or placebo [21]. They demonstrated shock reversal as well as survival benefit at 6 days, but the effects disappeared after 10 days. Luce et al. [22] found no improvement in survival or incidence of ARDS when they compared methylprednisolone Vs placebo in 75 septic patients. Two large, multicentre trials of steroids in sepsis were published in 1987. The Veterans Administration trial [23] randomized 233 patients to receive methylprednisolone 30 mg/kg followed by 5 mg/kg or placebo, administered within 3 hours of diagnosis. No difference in 14-day mortality or complications was demonstrated. Bone et al. [24], in their study of 381 patients, showed that methylprednisolone, 30 mg/kg was associated with higher mortality compared to placebo. Following these pivotal studies, the use of early, high dose corticosteroids in severe sepsis and septic shock fell out of favor.

Low dose steroids – a novel concept

In spite of disappointing results with the use of early, high-dose steroids there was continued interest in the use of more physiological doses. This was based on the assumption, that steroids, with their very powerful anti-inflammatory properties, could possibly be beneficial in a syndrome characterized by an uncontrolled pro-inflammatory response. The use of lower doses, could possibly lead to less damage to the host defense system and result in a reduced incidence of secondary infections. Anecdotal reports of improved lung function with steroids in patients with unresolving fibro-proliferative ARDS lent further support to this theory [25,26]. Bollaert et al. [27] conducted a prospective, double-blind, placebo controlled, randomized controlled trial comparing hydrocortisone, 100 mg/kg thrice a day for 5 days Vs placebo in 42 patients with septic shock who required vasopressor therapy after 48 hours. They found that shock reversal, defined as maintenance of systolic BP more than 90 mm of Hg with no requirement for vasopressor support or fluid resuscitation and a lactate level of less than 2 mmol/L were achieved to a significantly greater degree in the hydrocortisone group. The 28 day mortality tended to be lower in the steroid group (32% Vs 63%, $p = 0.045$). There was no significant morbidity associated with the use of steroids. In a study that appeared the following year, Briegel et al. [28] conducted a prospective, double-blind, placebo controlled trial, comparing hydrocortisone, 200 mg IV bolus followed by an infusion of 0.18 mg/kg/hr for at least 6 days, then tapered at the rate of 24 mg/day Vs placebo in 40 patients with vasopressor dependent septic shock. Though the majority of patients in both groups attained shock reversal and there was no change in mortality, there was earlier resolution of organ dysfunction in the steroid group. In their study of 40 patients with septic shock, Yildiz et al. [29] compared intravenous prednisolone 5 mg at 0600 hrs and 2.5 mg at 1800 hrs Vs placebo. Twenty eight day mortality was 8/20 (40%) in the steroid group Vs 12/20 (60%) in the placebo group ($p = 0.343$). The mortality rates in patients with occult adrenal insufficiency, defined as failure to increase cortisol



REVIEW OF PAPERS ON LACK OF BENEFIT OF EARLY, HIGH-DOSE CORTICOSTEROIDS IN SEVERE SEPSIS AND SEPTIC SHOCK

TABLE 2. RANDOMIZED CONTROLLED TRIALS ON LOW DOSE STEROIDS FOR SEPTIC SHOCK

Study	Methods	Participants	Interventions	Outcome	Comments
Bollaert, 1998	Randomized, two centers, double blind	n = 41, vasopressor dependent septic shock	Hydrocortisone 300 mg/day	Shock reversal at day 7, 28 day mortality, complications	Absolute difference in shock reversal = + 47% and in 28-day mortality = - 31%. No increased complications
Briegel, 1999	Randomized, one centre, double blind	n = 40, vasopressor dependent septic shock	Hydrocortisone, 100mg bolus, 0.18mg/kg/hr x 6 days, then tapered	Shock reversal at day 7, 28-day mortality, complications	Absolute difference in shock reversal = +25%, no difference in 28 day mortality, no increased complications
Yildiz, 2002	Randomized, one center, double blind	n = 40, vasopressor dependent septic shock	Prednisolone 5mg IV at 0600 hrs and 2.5 mg IV at 1800 hrs x 10 days	28 day mortality, complications	Trend towards, but non-significant reduction in 28 day mortality. No increased complications
Annane, 2002	Randomized, placebo ˘ controlled, double blind	n = 299, vasopressor dependent septic shock	Hydrocortisone 200mg/d + fludrocortisone 50 ±g/d x7days	Shock reversal at day 7, 28 day mortality	Shock reversal = +20%, mortality-10%

level by more than 20m±g/dl after ACTH stimulation, were 40% (2 of 5) in the steroid therapy group and 55.6% (5 of 9) in the standard therapy group, respectively (X^2 = 0.311, P = 1). Annane and colleagues [30] enrolled 299 patients in a multicentre, prospective, randomized, double blind trial. The treatment arm received a combination hydrocortisone 50 mg 6 hourly and fludrocortisone 50±g daily through a nasogastric tube for 7 days. A short ACTH stimulation test was done on all patients and non responders were defined as those who failed to increase their basal cortisol by 9±g/dl. The primary end point of the study was 28 day survival in non responders. Two hundred and twenty nine (76.6%) of patients were found to have occult adrenal insufficiency. The use of steroids in these patients was associated with improved survival ˘ there were 73 deaths in the placebo group (63%) as against 60 (53%) in the steroid treated group (RR, 0.83; 95% CI, 0.66 ˘ 1.04; adjusted OR, 0.54; CI, 0.31 ˘ 0.97; p = 0.04). Among responders, there was no significant effect of corticosteroids on 28 day, ICU, hospital or 1 year mortality. The authors concluded that a 7 day steroid replacement therapy resulted in improved survival in patients with septic shock with occult adrenal insufficiency.

Summary

Currently, there is enough evidence to suggest that early, high dose corticosteroid therapy has no place in the treatment of severe sepsis and septic shock. Small RCTs from the late 90 s do suggest some benefit with lower, physiological doses of corticosteroids, in terms of restoration of hemodynamic stability, resolution of organ dysfunction, and possibly, mortality. However, several unanswered questions remain as to the mechanism of the beneficial effects, the type of patients that will likely benefit, the best agent, dose, timing and duration of this therapy. Large, multicenter RCTs will be required before definite conclusions can be drawn. However, low dose corticosteroids should be considered every patient with septic shock, who does not respond adequately to increasing doses of vasopressors while carefully weighing the benefits and risks of this promising new therapy.

This paper was presented at Criticare2004, The 10th annual congress of the Indian Society of Critical Care Medicine, February 4-8, 2004, at the NCPA complex Bombay, India.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: the ACCP/SCCM Consensus Conference Committee, American College of Chest Phyisicians/Society of Critical Care Medicine. Chest 101:1644-1655
2. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B (1995) Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. JAMA 274:968-974
3. Chrouses GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332:1351-1362
4. Briegel J, Jochum M, Gippner-Steppert C, Thiel M (2001) Immunomodulation in septic shock: hydrocortisone differentially regulates cytokine responses. J Am Soc Nephrol 12 Suppl 17:S70-74
5. Abraham E (1999) Why immunomodulatory therapies have not worked in sepsis? Intensive Care Medicine 25:556-566
6. Reinhart K, Menges T, Gardlund B, Harm Zwaveling J, Smithes M, Vincent JL, Tellado JM, Salgado-Remigio A, Zimlichman R, Withington S, Tschaikowsky K, Brase R, Damas P, Kupper H, Kempeni J, Eiselstein J, Kaul M (2001) Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study. Crit Care Med 29:765-769
7. Jantz MA, Sahn SA (1999) Corticosteroids in acute respiratory failure. Am J Respir Crit Care Med 160:1079˜1100
8. Flower RJ (1986) The mediators of steroid action. Nature 320:20
9. Chin R, Eagerton DC, Salem M (1994) Corticosteroids. In: Chernow B (Ed) The Pharmacologic Approach to the Critically ill Patient. 3rd edn. Williams & Wilkins, Philadelphia, pp 715-737
10. Reichlin S (1993) Neuroendocrine-immune interactions. N Engl J Med . 329:1246-1253
11. Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 332:1351-1362
12. Pugeat M, Bonneton A, Perrot D, Rocle-Nicolas B, Lejeune H, Grenot C, Dechaud H, Brebant C, Motin J, Cuilleron CY (1989) Decreased immunoreactivity and binding activity of corticosteroid-binding globulin in serum in septic shock. Clin Chem. 35:1675-1679
13. Firschein HE, De Venuto F, Fitch WM, Pearce EM, Westphal U (1957) Distribution of injected cortisol-4-C^{14} in normal and shocked rats. Endocrinology. 60:347-358
14. Melby JC, Spink WW (1958) Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. J Clin Invest. 37:1791-1798
15. Knighton JD, Woodcock TE, Hough M (1999) Adrenal failure in the critically ill. Br. J Anaesth 82:152-153
16. Rothwell PM, Lawler PG (1995) Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med. 23:78-83
17. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E (2000) A 3-Level Prognostic Classification in Septic Shock Based on Cortisol Levels and Cortisol Response to Corticotropin. JAMA 283(8): 1038-1045
18. Annane D, Bellissant E, Sebille V, Lesieur O, Mathieu B, Raphael JC, Gajdos P (1998) Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 46:589˜597
19. Briegel J (2000) Hydrocortisone and the reduction of vasopressors in septic shock: therapy or only chart cosmetics? Intensive Care Med 26:1723˜1726
20. Schumer W (1976) Steroids in the treatment of clinical septic shock. Ann Surg 184:333˜339
21. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M (1984) The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. N Engl J Med 311:1137-1143
22. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF (1988) Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 138:62˜68
23. (1987) Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis The Veterans Administration Systemic Sepsis Cooperative Study Group. N Engl J Med 317:659˜665
24. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653˜658
25. Meduri GU, Kanangat S (1998) Glucocorticoid treatment of sepsis and acute respiratory distress syndrome: time for a critical reappraisal. Crit Care Med 26:630˜633
26. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA (1998) Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 280:159˜165
27. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A (1998) Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26:645˜650
28. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K (1999) Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 27:723˜732
29. Yildiz O, Doganay M, Aygen B, Guven M, Keleutimur F, Tutuu A (2002) Physiological-dose steroid therapy in sepsis. Crit Care 6:251-259
30. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862˜871