—Review—

Controversy of Corticosteroids in Septic Shock

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Abstract

The mortality rate of septic shock remains high. The guidelines of the Surviving Sepsis Campaign were published in 2004 and were revised in 2008. Steroid therapy is prominent in the guidelines but remains controversial. In this review, steroid therapy for septic shock is discussed with various landmark papers.
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Key words: Surviving Sepsis Campaign, corticosteroids, septic shock

Introduction

The mortality rate of severe sepsis and septic shock in most centers remains high despite recent advances in intensive care treatment. In 2004 an international group of critical care and infectious disease physicians specializing in the diagnosis and management of infection and sepsis met to develop sepsis campaign guidelines for the management of severe sepsis and septic shock which could be used by clinicians at the bedside to improve outcomes in severe sepsis and septic shock[1,2]. A revised version of the guidelines was published in 2008[3,4]. In the revised guidelines, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to guide the assessment of the quality of evidence from high (A) to very low (D) and to determine the strength of recommendation. A strong recommendation, "recommend," indicates that an intervention's desirable effects clearly outweigh its undesirable effects (risk, burden, cost). A weak recommendation, "suggest," indicates that the tradeoff between desirable and undesirable effects is less clear. Among the revisions, corticosteroids are prominent. Corticosteroid therapy for severe sepsis and septic shock has been controversial, and, therefore, we must be alert to the evidence and be careful to follow the guidelines. In this review, affirmative and negative views on corticosteroid therapy in septic shock are discussed.

History of Corticosteroids in Septic Shock

In 1976 Schumer reported that high doses of methylprednisolone and dexamethazone improve survival rates in patients with septic shock[5]. Since then, many groups have studied the effects of corticosteroids in severe sepsis and septic shock, and corticosteroids had been used before a consensus was reached. The controversy is due in part to the lack of definitions for "sepsis," "severe sepsis," and "septic shock," and then Bone, et al. reached a consensus in defining the terminology[6,7]. Eleven years later, Bone, et al. reported in *The New England Journal of Medicine* that a double-blind, randomized, controlled trial showed that a large dose of methylprednisolone (30 mg/kg) increased the

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Table 1 Summary of Steroids/ Surviving Sepsis Campaign 2008

- Consider intravenous hydrocortisone for adult septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors. (2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone. (2B)
- Hydrocortisone is preferred to dexamethasone. (2B)
- Fludrocortisone (50 μg orally a day) may be included if an alternative to hydrocortisone is being used when lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used. (2C)
- Steroid therapy may be warranted once vasopressors are no longer required. (2D)
- Hydrocortisone dose should be ≤300 mg/day. (1A)
- Do not use corticosteroids to treat sepsis in the absence of shock unless patient's endocrine or corticosteroid history warrants it. (1D)

Reference 3, 4

mortality rate of patients with severe sepsis and septic shock[8]. This report was so influential that steroid therapy shock became less popular as a first line treatment for septic shock.

In 2000, Annane et al. reported that septic shock might be associated with relative adrenal insufficiency. This new insight provided a physiological rationale for corticosteroid treatment for septic shock. Thus, replacement therapy with low doses of corticosteroids was again proposed to treat septic shock[9]. In their placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France, Annane et al found that treatment with hydrocortisone (50 mg intravenous bolus every 6 hours) and fludrocortisone (a 50 μg tablet once daily) for 7 days significantly reduced mortality rates in patients with septic shock and relative adrenal insufficiency without increasing the rate of adverse events[10]. On the basis of this evidence, the Surviving Sepsis Campaign (SSC) Guidelines of 2004 recommended intravenous corticosteroids (hydrocortisone, 200–300 mg/day for 7 days in 3 or 4 divided doses or by continuous infusion) for patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure. A 250 μg ACTH stimulation test was recommended to identify responders (>9 μg/dL rise in cortisol 30–60 minutes after ACTH administration), and intravenous corticosteroids were discontinued in these patients[1,2].

SSC Guidelines 2008 and Subsequent Developments

The SSC Guidelines 2008 recommend intravenous hydrocortisone for adult patients with septic shock when hypotension remains poorly responsive to fluid resuscitation and vasopressors[3,4]. Recommendations and suggestions regarding steroids therapy are summarized in **Table 1**. Almost simultaneously, a multicenter, randomized, double-blind, placebo-controlled trial (the Corticosteroid Therapy of Septic Shock [CORTICUS] study) was assessing the efficacy of corticosteroids in septic shock. Following the SSC Guidelines 2008, the results of the CORTICUS study were published in *The New England Journal of Medicine*, and the effects of corticosteroids in septic shock were refuted[11]. The CORTICUS study of 499 patients showed that hydrocortisone (50 mg of intravenous hydrocortisone every 6 hours for 5 days) did not improve the 28-day survival rate or the rate of reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened the reversal of shock in patients in whom shock was reversed. However, differences in clinical characteristics between the French study and the CORTICUS study produced critical differences in their results. For example, the baseline levels of severity differed. Therefore, the 28-day mortality rates in the placebo groups differed between the studies. Furthermore, the percentages of surgical patients differed. In these patients, source control might be more important. Thus, because of these differening factors, these studies disagreed. In the

Table 2 Summary of Consensus Statements

- Hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those patients who have responded poorly to fluid resuscitation and vasopressor agents. (Grade 2B)
- The ACTH stimulation test should not be used to identify those patient with septic shock or ARDS who should receive glucoroticoids. (Grade 2B)
- Intravenous hydrocortisone should be given in a dose of 200 mg/day in four divided doses or as bolus of 100 mg followed by a continuous infusion at 10 mg/hr (240 mg/day). (Grade 1B)
- Patients with septic shock should be treated for ≥7 days before tapering, assuming that there is no recurrence of signs of sepsis or shock. (Grade 2B)
- Dexamethasone is not recommended for the treatment of septic shock. (Grade 1B)
- Treatment with fludrocortisone (50 μg orally once daily) is considered optional. (Grade 2B)

Reference 12

same year, recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adults were published in *Critical Care Medicine*[12]. These recommendations are consensus statements of an international task force assembled by the American College of Critical Care Medicine. The task force advocated the term "critical illness-related corticosteroid insufficiency" to describe the dysfunction of the hypothalamic-pituitary-adrenal axis during critical illness. In the statements, the benefit of treatment with glucocorticoids at this time seems to be limited to patients with vasopressor-dependent septic shock. The adrenocorticotropin test should not be used to identify those patients with septic shock who should receive glucocorticoids. Hydrocortisone, at 200 mg/day in 4 divided doses or at 240 mg/day as a continuous infusion (10 mg/hour) for 7 days, is recommended for septic shock. Glucocorticoids should be tapered rather than stopped abruptly. Dexamethasone is not recommended to treat critical illness-related corticosteroid insufficiency (**Table 2**).

How Can We Consider Corticosteroid Treatment in Septic Shock?

Immediately after SSC Guidelines 2008 were published, the CORTICUS study refuted the effects of corticosteroids in septic shock. Therefore, there was no consensus regarding the recommendations for the use of corticosteroids in septic shock described in the SCC Guidelines 2008. However, the CORTICUS study demonstrated that hydrocortisone hastened the reversal of shock in patients when shock was reversed. Consequently, the corticosteroid therapy recommended in the Consensus statements published in *Critical Care Medicine* in 2008 appears to be the most acceptable. Most studies were designed to have the 28-day prognosis as the primary end point, but the effects of corticosteroids should be evaluated on the basis of the reversal of shock. Hastened reversal of shock due to corticosteroids might have the advantage of providing other therapeutic options. For example, surgical source control can be effectively performed only when the blood circulation is stable. Successful treatment following a rapid reversal of shock may result in immediate recovery. On the other hand, a prolonged state of shock may preclude various salvage treatments. In a majority of the cases, high 28-day mortality rate is due to uncontrolled sources of infection. However, we should be careful because corticosteroids may increase the severity of sepsis when infection sources are not sufficiently controlled.

Conclusion

There is a long history of controversy regarding corticosteroid therapy in septic shock. Most evidence was provided by studies outside Japan, and their subjects might not match the Japanese population in some respects, including gene polymorphisms[13,14]. Therefore, future studies should be designed with a consideration for genetic background. Most importantly, we should complete a Japanese multicenter prospective, randomized, double-blind, controlled trial. Otherwise, we may not reach a true consensus. Presently, it is proposed that the effects of corticosteroids must be carefully discussed in each clinical setting before they are used.

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