DOI: 10.4274/tjem.2408

Steroid Use in Sepsis

Sepsiste Steroid Kullanımı

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Abstract

Sepsis is defined as "systemic signs and symptoms of infection in the presence of infection". Nearly one fourth of sepsis cases eventually die. Therefore, rapid and correct management of sepsis is important. There is no reliable test to evaluate adrenal insufficiency in sepsis due to the changes in the hypothalamic-pituitary-adrenal axis and intracellular effects of cortisol during the critical illness. Clinical studies reported conflicting results regarding the effects of steroid therapy on mortality and morbidity in sepsis. Contemporary sepsis management guidelines - although not based on strong evidence - suggest consideration of steroid use in septic patients who do not respond to intravenous fluids and vasopressors. Stronger evidence obtained from randomized controlled trials is needed for this suggestion to be certain. *Turk Jem 2013; 17: 121-124*

Key words: Sepsis, steroid, adrenal failure

Özet

Sepsis, enfeksiyon varlığında, enfeksiyonun sistemik belirti ve bulgularının olması olarak tanımlanır. Sepsis olgularının yaklaşık dörtte biri ölümle sonuçlanmaktadır. Bu nedenle hızlı ve doğru sepsis yönetimi önemlidir. Kritik hastalık sürecinde hipotalamo-hipofizyo-adrenal aksta ve kortizolün hücre içi etkinliğinde olan değişiklikler nedeniyle, sepsiste adrenal yetmezliği değerlendirmek için güvenilir bir laboratuvar testi bulunmamaktadır. Klinik araştırmalar sepsiste steroid tedavisinin morbidite ve mortaliteye etkileri konusunda çelişkili sonuçlar yayınlanmıştır. Güncel sepsis tedavi kılavuzları, güçlü kayıtlara dayanmasa da, sıvı ve vazopressör tedaviye yanıtı olmayan sepsis hastalarında steroidin düşünülmesini önermektedirler. Bu önerinin kesinlik kazanması için randomize kontrollü çalışmalardan elde edilmiş daha güçlü kanıtlara ihtiyaç vardır. *Turk Jem 2013; 17: 121-124*

Anahtar kelimeler: Sepsis, steroid, adrenal yetmezlik

Introduction

Sepsis is the appearance of systemic signs and symptoms of the infection, in the presence of the infection. Severe sepsis is sepsis complicated by deterioration of tissue perfusion and organ dysfunction. Septic shock occurs when hypotension in patients with sepsis does not improve despite the proper hydration (1).

Approximately one-quarter of sepsis cases are fatal (2,3). Therefore quick and accurate sepsis management is crucial.

The first animal experiments published nearly forty years ago showed that steroid therapy improved survival in endotoxic shock. As a result of those studies, steroid therapy was started to be addressed in clinical trials (4,5).

Steroid dose used in some of the clinical trials was increased up to 30-120 mg/kg/day of methylprednisolone or equivalent. However, the negative results of the treatment at this dose were observed as well. In fact, a meta-analysis has proved that high-dose steroids increases mortality in septic patients (6). But in subsequent years, clinical studies have revealed ample evidence on the benefits of physiological doses of steroids (7,8,9,10,11).

What changes in the HPA Axis in cases of critical illness?

Exposure to stress starts a series of responses that are interrelated in organism, but also complex, and have central and peripheral terminals. These responses are intended to increase survival. This phenomenon, known as stress response, is governed by two principal systems; sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA) (12). Due to the activation of the HPA axis, steroid synthesis increases and as such, steroid regulates immune, cardiovascular and metabolic changes in order to cope with stress.

The primary glucocorticoid secreting by the adrenal cortex is cortisol. Cortisol is not a hormone stored in the adrenal and it has a half-life of 70 to 120 minutes (13). In the circulation, 90% of cortisol is transported by cortisol-binding globulin (CBG) (13). In the cell, cortisol binds to the intracellular glucocorticoid receptor (GR). With this binding, steroid-receptor complex gets activated and moves to the nucleus. In the nucleus, steroid-receptor complex binds to the particular regions in DNA that are called glucocorticoid response elements (GRE). Consequently, the transcription of the related

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genes and protein synthesis are carried out as such (15) (Figure 1). Besides managing the transcription process in thousands of genes, cortisol may intervene with other transcription factors as well. The most significant of these is nuclear factor kappa beta (NF-κB). NF-κB is responsible for the synthesis of important cytokines such as the interleukins and tumor necrosis factor, and inhibits cortisol NF-κB (16).

It was found that, in acute disease, some changes occurred in cortisol's production, transportation and cellular effects. In acute disease, CBG levels are decreased by almost half and the free cortisol levels are increased (17). In experimental models, pro-inflammatory cytokines and endotoxins have been shown to decrease the number of GR, GR's translocation, and the affinity of the steroid receptor complex to DNA. This situation indicates that steroid resistance, usually observed during chronic inflammatory conditions like chronic obstructive pulmonary disease, might be present in the acute inflammation as well. In another study, it has been proven that cortisol, measured from the interstitium by microdialysis method, only moderately correlates with plasma cortisol (18). This means that cortisol levels in the circulation are not necessarily a direct indicator of its effects in the tissue.

These changes complicate the task of defining the adrenal insufficiency in sepsis. But the challenges facing clinicians are not limited with these. Usually, adrenal insufficiency is diagnosed through the ACTH stimulation test. 9 mcg/dl or more increase in cortisol (delta cortisol) following a 250 mcg intravenous ACTH excludes the diagnosis of adrenal insufficiency (19). Studies shows that steroid therapy reduces mortality in patients with sepsis, who were diagnosed with adrenal insufficiency by using this test (7,9). However, study results published recently has suggested that this test might not be reliable. Investigating the effects of steroid therapy in patients with sepsis, this multicenter, randomized, controlled study has been shown that steroid therapy has no effect on mortality whether or not the patient responds to ACTH (20). ACTH stimulation test might give an idea about the function of the adrenal glands but does not reveal whether the HPA axis is normal or not. For this reason, manuals do not recommend steroid therapy to be planned based on the ACTH stimulation test in septic patients (21,22).

Likewise, the measurements of free cortisol levels are not recommended in the manuals (21,22). The reason behind this is the fact that the free cortisol measurement cannot be performed in every laboratory. In addition, the normal level of free cortisol in septic patients has not yet been clearly established. Etomidate, that is used in the intensive care for induction of anesthesia prior to the intubation, is also known to suppress the HPA axis (23).

All of these factors clearly show that, there is no good laboratory test in the hands of clinicians to diagnose the relative or absolute adrenal insufficiency. A guide published in 2008 has been proposed the "critical illness associated adrenal insufficiency" as a definition instead of "relative or absolute adrenal insufficiency" (22). This definition includes both the lack of adrenal steroid production and the immeasurable changes in tissue levels; and does not specify a threshold laboratory value.

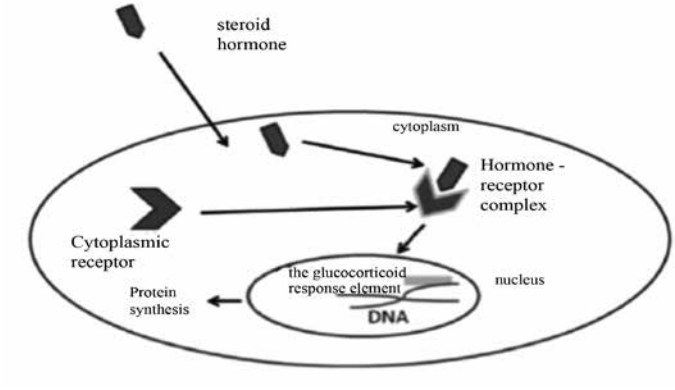

Figure 1. Mechanism of action of steroid

Clinical Trials and Meta-Analyses

Regarding the use of steroids in sepsis, there are numerous clinical studies with different results. In recent years these studies have been examined through meta-analyses. In a compilation including 12 studies, Annane et al. report that low-dose hydrocortisone accelerates the recovery time from the shock and remarkably reduces 28-day mortality rate (RR, 0.84; 95% CI, 0.72-0.97, p=0.02). (6) Minecci et al. has obtained similar results in their meta-analysis (24). In another meta-analysis, Sligl et al. was more selective in choosing the cases and evaluated 8 studies (6 of them being good level randomized, controlled studies), and argued that steroid accelerates the recovery from the shock but it has no effect on mortality (RR, 1.00; 95% CI, 0.84 to 1.18) (25). In sepsis manual published in 2013, according to an assessment among evidences, in three of the 6 selected studies which used hydrocortisone for sepsis treatment, mortality was relatively lower than the others but in these studies hydrocortisone therapy had no effect on mortality. In the other three studies with higher mortality, a non-significant reduction in mortality was observed (22).

Out of the two most comprehensive studies regarding the use of steroids in sepsis, the first one is the multicenter study of Annane and colleagues held in France, and the other is a multicenter study called CORTICUS that was conducted in Europe. Both studies were designed as randomized, double-blind, and placebo controlled.

Annane et al. worked with 300 patients with sepsis. To septic shock patients, who are not responding to vasopressors, 4x50 mg hydrocortisone and 50 mcg fludrocortisone treatment was administered for five days. This treatment had started within 8 hours after patients were diagnosed with sepsis. In this study, patients with delta cortisol lower than 9mcg/dl after ACTH stimulation test had been considered as non-responders. In ACTH non-responder cases, hydrocortisone treatment had been shown to accelerate the recovery time from the shock and reduce mortality (7). According to this study, there was no infection or an increased incidence of gastrointestinal bleeding in the steroid receiving group.

In CORTICUS, 500 patients with septic shock were included in the study. The use of hydrocortisone was started in the first 72 hours at a dose of 4x50 mcg. But in this study, it was proven that steroid has no effect on the mortality in any cases, whether responded to ACTH or not. Shock recovery appeared faster in the steroid receiving group despite their ACTH response. In the

Table 1. The comparison between the study of Annane et al. and CORTICUS	
The study of Annane et al.	**CORTICUS**
multi-centered in France	multi-centered in Europe
double-blind, randomized, placebo-controlled	double-blind, randomized, placebo-controlled
septic shock unresponsive to vasopressors	septic shock
first 8 hours	first 72 hours
N: 300	N: 500
28-day mortality rate is 61% in the placebo group	28-day mortality rate is 31% in the placebo group
Surgical patient 40%	Surgical patient 64%
4x50mg hydrocortisone and 50 mcg fludrocortisone	4x50mg hydrocortisone
Results: In patients with relative adrenal insufficiency, mortality decreased by 30%	Results: no difference in mortality independent from ACTH (250mcg) test
	Faster shock recovery in the treatment group (ACTH responsive group)
	High risk of new infection and recurrence of inflammation (rebound shock), (not statistically significant)

steroid group, the recurrence of shock and the risk of infection was increased, though statistically insignificant. CORTICUS authors do not recommend steroid therapy in septic shock (20).

The comparative summary of these two studies is shown in Table 1. In CORTICUS, the 28-day mortality rate is lower in the placebo cases, that is, it can be said that this study includes sepsis patients in relatively good conditions. In CORTICUS, the ratio of surgical patients is higher. Between this study and the one held in France, the main differences are the latter's inclusion of only sepsis patients with no vasopressors response, the rapid initiation of the treatment and the high mortality in the placebo group.

What does manuals say?

Current clinical approach to the diagnosis and treatment of adrenal insufficiency associated with sepsis:

The American Critical Care Medicine Manual was published in 2008. This manual proposes the consideration of hydrocortisone treatment in patients with septic shock who have no response to fluid and vasopressor therapy. Authors have been described this proposal as a recommendation based on weak and/or moderate evidence (22). Recommended diagnostic threshold of this guide is 10 mcg/dl or lower cortisol level or a cortisol increase (delta cortisol) of lower than 9 mcg/dl after the cosintrophyn test. As the threshold in sepsis patients is not known, free cortisol measurement is not recommended. Regarding the dose, this guide recommandes a 200 mg/day of hydrocortisone in four divided doses or 10mg/hour infusion after 100mg bolus hydrocortisone (240 mg).

The sepsis manual of Canadian Association of Emergency Physicians, that was published in the same year, repeats the same recommendations regarding which patient should be given steroids. This is a Level D recommendation, which means that it was based on contradictory results (26). Hydrocortisone dose recommended by this manual is 200-300 mg/day. Administration of an ACTH stimulation test before medical treatment is optional, but steroids should be given based on the clinical requirements prior to the test results. Canadian manual recommends 4-6 mg intravenous dexamethasone to emergency physicians as another option. In this situation, tests can be administered later as dexamethasone does not affect ACTH and serum cortisol.

In 2010, the German Hematology Oncology Association published a guide not recommending the steroid use for sepsis in neutropenic patients, a suggestion based on moderate contradictory evidence (27).

The most comprehensive and up to date manual about sepsis was published in February 2013. This guide proposes the consideration of hydrocortisone in septic shock patients with no response to fluid and inotropic agents. This is a Level C recommendation, that means a low-level evidence-based, weak suggestion (21). Recommended dose is 200 mg/day hydrocortisone. Authors argue that in patients with sepsis, cortisol measurement tests conducted anytime in patient's history would not reveal accurate results and ACTH stimulation test is unnecessary. Steroid therapy should be tapered slowly after the elimination of the need for vasopressors.

Conclusion

Sepsis is a complex process affecting many systems and involves different response mechanisms. In septic patients, steroids, both in the HPA axis and intracellularly, are dissimilar to a healthy person. Thus there is no reliable test to detect the steroid sufficiency in sepsis. Clinical studies give conflicting information about the effects of steroids in sepsis mortality. In the light of current manuals, steroid therapy is thought to be appropriate to sepsis patients whose hypotension does not improve despite proper support for vasopressor and the proper hydration. Yet stronger evidence derived from randomized controlled trials are necesssary to define this treatment as conclusive.

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