Research
Physiological-dose steroid therapy in sepsis [ISRCTN36253388]

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Abstract

Introduction The aim of the study was to assess the prognostic importance of basal cortisol concentrations and cortisol response to corticotropin, and to determine the effects of physiological dose steroid therapy on mortality in patients with sepsis.

Methods Basal cortisol level and corticotropin stimulation test were performed within 24 hours in all patients. One group (20 patients) received standard therapy for sepsis and physiological-dose steroid therapy for 10 days; the other group (20 patients) received only standard therapy for sepsis. Basal cortisol level was measured on the 14th day in patients who recovered. The outcome of sepsis was compared.

Results Only Sequential Organ Failure Assessment (SOFA) score was found related to mortality, independent from other factors in multivariate analysis. No significant difference was found between the changes in the percentage of SOFA scores of the steroid therapy group and the standard therapy group in survivors, nor between the groups in basal and peak cortisol levels, cortisol response to corticotropin test and mortality. The mortality rates among patients with occult adrenal insufficiencies were 40% in the steroid therapy group and 55.6% in the standard therapy group.

Discussion There was a trend towards a decrease in the mortality rates of the patients with sepsis who received physiological-dose steroid therapy. In the advancing process from sepsis to septic shock, adrenal insufficiency was not frequent as supposed. There was a trend (that did not reach significance) towards a decrease in the mortality rates of the patients with sepsis who received physiological-dose steroid therapy.

Keywords adrenal insufficiencies, cortisol, occult adrenal insufficiencies, physiological-dose steroid therapy, sepsis

Introduction

This paper was presented at the 10th European Congress of Clinical Microbiology and Infectious Diseases (28–31 May 2000, Stockholm, Sweden).

Sepsis can be defined as a systemic response to infection [1]. The incidence of sepsis worldwide is on the increase. Sepsis and its sequels are the leading causes of death in intensive care units. Mortality rates are higher for patients with pre-existing disease, medical conditions, care in the intensive care unit, and multiple organ failure [2,3]. Despite steady improvements in antibiotic therapy and intensive care management during the past decade, mortality has remained close to 50%. This high mortality rate has continued to stimulate interest in pharmacological agents that might reduce morbidity and mortality [4–7].

AI = adrenal insufficiency; APACHE = Acute Physiology and Chronic Health Evaluation; ACTH = corticotropin; CI = confidence interval; OR = odds ratio; SOFA = Sequential Organ Failure Assessment.

Steroid therapy in patients with sepsis is still controversial. In the 1960s, stress doses of hydrocortisone for the treatment of sepsis were investigated, but no advantages could be shown in a double-blind multicenter study [8]. This led to the discontinuation of steroid replacement therapy for sepsis. In the 1970s, therapy with pharmacological doses of glucocorticoids was widely used in patients with sepsis and septic shock. The most compelling evidence in favor of corticosteroid treatment was reported by Schumer [9] in his prospective randomized study of steroid administration to patients with septic shock. These data indicate that methylprednisolone (30 mg/kg) or dexamethasone (3 mg/kg) reduced the mortality rate from 38.4% to 10.5%. However, later in the mid-1980s, pharmacological doses of glucocorticoids for the treatment of sepsis were investigated extensively until several clinical trials gave negative results [10–12]. Moreover, there is some evidence that the use of high-dose glucocorticoids in sepsis might be harmful [11].

Many studies have demonstrated that elevated cortisol levels in sepsis and the degree of elevation are related to the severity of illness [13]. Basal and corticotropin (ACTH)-stimulated cortisol levels correlate with the severity of illness, and very high cortisol levels often signify a poor prognosis [14]. In sepsis, the hypothalamic–pituitary–adrenal axis is activated through systemic and neural pathways. Circulating cytokines such as tumor necrosis factor α, interleukin-1 and interleukin-6 activate the hypothalamic–pituitary–adrenal axis independently and, when combined, have synergistic effects [15].

Sepsis can also cause adrenal insufficiency (AI), which is associated with increased mortality [16]. In recent years, several authors have proposed a syndrome of occult AI in septic shock in the presence of normal or even elevated serum cortisol concentrations. This hypothesis is based on many studies investigating the adrenocortical response of patients with septic shock to 0.25 mg of ACTH. Up to 28% of seriously ill patients have been suggested to have occult or unrecognized AI [14]. The prevalence of occult AI (a cortisol increment after a short ACTH test of less than 9 mg/dl) in severe sepsis was estimated at about 50% and the 28-day mortality rate at about 75% [17]. A few studies have indicated that stress doses of hydrocortisone improve hemodynamics in patients with hyperdynamic septic shock, which is unresponsive to conventional therapy [18,19]. However, the use of a physiological dose of steroid in patients with sepsis, severe sepsis, and septic shock has not yet been completely evaluated. We therefore performed a placebo-controlled, randomized, double-blind, single-center study.

The aim of this study was to assess basal cortisol concentrations and the cortisol response to ACTH stimulation as well as their prognostic importance, and also to determine the effects of the physiological-dose steroid therapy on mortality in patients with sepsis.

Methods

Study design

The study protocol was approved by the Institutional Review Board of Erciyes University and informed consent was obtained from the patients' relatives. This placebo-controlled, randomized, double-blind, single-center study was performed at the Department of Medical Intensive Care Unit and the Department of Infectious Diseases of Erciyes University Medical School during a 2-year period (from May 1997 to April 1999).

Patient selection

Patients over 17 years old and diagnosed with sepsis were included consecutively in the study. The diagnosis of sepsis was based on the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Report [1]. The severity of illness was classified according to this definition (Table 1).

Criteria for exclusion from the study were as follows: already known pre-existing adrenal disease or adrenalectomy, known malignancies, tuberculosis that might have involved the adrenal gland, and administration of steroids within the 3 months before the admission. In addition, patients with burns, hemorrhagic shock or those who had suffered myocardial infarction were not included.

Treatment protocol

Patients enrolled in the study were treated with standard therapy used in the treatment of sepsis and septic shock. This therapy could include the following: administration of antibiotics, fluid replacement, vasoactive drugs, mechanical ventilatory support, and any other form of supportive therapy deemed necessary by the primary physicians. Soon after the presumptive diagnosis of severe sepsis, initial laboratory specimens were obtained and within 2 hours the patients were randomized to treatment with prednisolone or placebo groups. The treatment groups were determined by a computer-generated randomization procedure. The steroid therapy group received prednisolone at a physiological dose. Prednisolone was given intravenously at 06.00 (5 mg) and 18.00 (2.5 mg) for 10 days. The standard therapy group received a placebo infusion containing physiological saline solution in an identical manner. Patients and their primary physicians were blinded as to which therapy was administered.

Data collection

An ACTH stimulation test was performed with 250 μg of tetracosactrin (synacthene; Ciba Geigy, Germany) given intravenously. Blood samples were taken immediately before the test and at 30 and 60 minutes afterwards. After centrifugation, plasma samples were stored at −20°C until assayed. ACTH stimulation test was repeated on the 14th day in the patients who survived. Plasma cortisol concentrations were determined by radioimmunoassay with a commercially available kit (ICN Biomedicals, Inc, Costa Mesa, California, USA).

Table 1

Consensus conference group definitions of the stages of sepsis [1]

I. Systemic inflammatory response syndrome (SIRS)

Two or more of the following:

Temperature of more than 38°C or less than 36°C

Heart rate of more than 90/min

Respiratory rate of more than 20/min

White blood cell count of more than 12,000/mm^3 or less than 4000/mm^3 or more than 10% immature forms (bands)

II. Sepsis

Systemic inflammatory response syndrome plus a culture-documented infection

III. Severe sepsis

Sepsis plus organ dysfunction, hypotension, or hypoperfusion (including but not limited to lactic acidosis, oliguria, or acute alteration in mental status)

IV. Septic shock

Hypotension (despite fluid resuscitation) plus hypoperfusion abnormalities

Intra-assay coefficients of variation were for control A 7.0%, control B 5.8%, and control C 5.1%. Inter-assay coefficients of variation were for control A 7.9%, control B 6.5%, control C 6.0%. The cortisol response was defined as the difference between the basal and peak cortisol concentrations. Normal adrenal function was defined as a plasma cortisol level (before or at 30 or 60 minutes after the injection of ACTH) above 20 µg/dl. The cases with peak cortisol levels lower than 20 µg/dl were considered to be AI [13,20–22]. Occult AI was defined as an increase in cortisol after a ACTH test of less than 9 µg/dl (a cortisol response of no more than 9 µg/dl) [17,23,24].

Community-acquired sepsis had its onset within 72 hours of the patients' admission to the hospital, whereas hospital-acquired sepsis began 72 hours or later after admission. The estimated prognosis of any pre-existing underlying diseases had been classified according to the classification of McCabe and Jackson [25].

Observed initial findings that related to disseminated intravascular coagulation, respiratory insufficiency, altered mental status, and renal, cardiac, and liver failure were noted [26,27]. The severity of the illness was assessed with the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system [28]. The Sequential Organ Failure Assessment (SOFA) score [29] was added to the study protocol by amendment and retrospectively from the raw data. Infections were diagnosed according to clinical and microbiological criteria. Blood samples for cultures were

obtained by the same investigator (O Yildiz) and inoculated into a standard culture medium (BACTEC 9240). Patients were evaluated at enrollment and at the 24th hour, and on the 3rd, 7th, 10th, 14th, 21st, and 28th days, and followed for 1 month after discharge from hospital.

Body temperature, respiratory rate, heart rate, blood pressure, the use of vasopressor drugs, urine output, complete blood counts, urinalysis with microscopic examination, erythrocytes sedimentation rate, blood chemistry, prothrombin time, partial thromboplastin time, fibrinogen, fibrin debranching product, blood gases, electrocardiogram, and chest roentgenogram were recorded for each patient individually.

Study endpoints

The primary endpoint of the study was 28-day mortality from all causes. The secondary endpoint consisted of adverse occurrences including possible complications of drug therapy and morbid events such as the progression of initial infection and the development of secondary infection. Secondary infection was defined as the identification of a new site of infection or the emergence of a different organism at the same site, generally requiring a change in antibiotic management.

All medications given to the patients, any complications, the duration of hospitalization, the mortality rate, and the causes of death were recorded and compared between the groups. We also compared average values of basal cortisol, peak cortisol and cortisol responses to ACTH between survivors and non-survivors on the first day. Moreover, basal cortisol levels on the 1st and 14th days were compared in patients who recovered in each group.

Statistical analysis

Student's t-test and the Mann–Whitney U multivariate analysis test were used for continuous variables, χ^2 and Fisher's χ^2 tests were used for proportions, and logistic regression was used for effects of factors on mortality. Values are expressed as means ± SD, odds ratio (OR) and 95% confidence interval (CI) or proportion.

Results

Description of study population

Forty patients with sepsis, severe sepsis and septic shock were included in this study. The mean age of patients was 56.5 ± 16.4 years in the standard therapy group and 57.8 ± 17.7 years in the steroid therapy group. There was no significant difference in demographic characteristics, the severity of underlying diseases, the APACHE II and SOFA scores, the median time to hospital and median time to death, the acquisition of infection, and the sepsis categories between the groups (Table 2).

The 28-day mortality

There were eight deaths (40%) in the steroid therapy group and 12 (60%) deaths in the standard therapy group

Table 2

Characteristics of patients

Variable	Steroid therapy group	Standard therapy group	Total	χ^2	P
All patients	20 (50%)	20 (50%)	40	0.417	0.748
Female	7 (43.8%)	9 (56.3%)	16		
Male	13 (54.2%)	11 (45.8%)	24		
Mean age (years) (mean ± SD)	57.8 ± 17.7	56.5 ± 16.4	57.1 ± 16.9		0.818
Underlying diseases	11 (40.7%)	16 (59.3%)	27	2.849	0.176
Rapidly fatal	–	–	–		
Ultimately fatal	2 (50%)	2 (50%)	4		
Nonfatal	9 (39.1%)	14 (60.9%)	23		
No underlying diseases	9 (69.2%)	4 (30.8%)	13		
APACHE II (mean ± SD)	15.4 ± 5.5	17.9 ± 8.0	16.6 ± 6.9		0.249
Maximum SOFA (mean ± SD)	7.8 ± 3.9	9.3 ± 4.0	8.5 ± 4.0		0.257
Acquisition of infection				0.143	1.000
Community	16 (51.6%)	15 (48.4%)	31		
Hospital	4 (44.4%)	5 (55.6%)	9		
Sepsis categories				0.456	0.531
Sepsis	8 (57.1%)	6 (42.9%)	14		
Severe sepsis	8 (47.1%)	9 (52.9%)	17		
Septic shock	4 (44.4%)	5 (55.6%)	9		
Positive cultures				2.345	>0.05
Gram-negative infection	4 (36.4%)	7 (63.6%)	11		
Gram-positive infection	10 (66.7%)	5 (33.3%)	15		
Candida infection	1 (33.3%)	2 (66.7%)	3		
Polymicrobial infection	3 (60.0%)	2 (40.0%)	5		
Negative cultures	6 (46.2%)	7 (53.8%)	13		
Organ failure	16 (47.1%)	18 (52.9%)	34		
DIC	5 (45.5%)	6 (54.5%)	11		
Laboratory measurements (mean ± SD)					
Leukocytes (/mm^3)	16,057 ± 12,568	14,781 ± 7,317			0.697
Platelets (/mm^3)	183,050 ± 137,983	192,800 ± 127,157			0.324
ESR (mm/h)	69 ± 36	49 ± 33			0.081
CRP (mg/l)	67 ± 16	67 ± 24			0.981
Fibrinogen (mg/dl)	814 ± 394	434 ± 198			0.002
Median stay in hospital (days)	14	13			0.406
	(95% CI 11.09–20.08)	(95% CI 10.13–16.37)			
Median time to death (days)	5	5.5			0.496
	(95% CI, 2.55–8.20)	(95% CI, 2.19–13)			
Non-survivors	8 (40%)	12 (60%)	20	1.600*	0.343
Survivors	12 (60%)	8 (40%)	20		

*Fisher's χ^2 test. CI, confidence interval; DIC, disseminated intravascular coagulation; ESR, erythrocytes sedimentation rate.

Figure 1
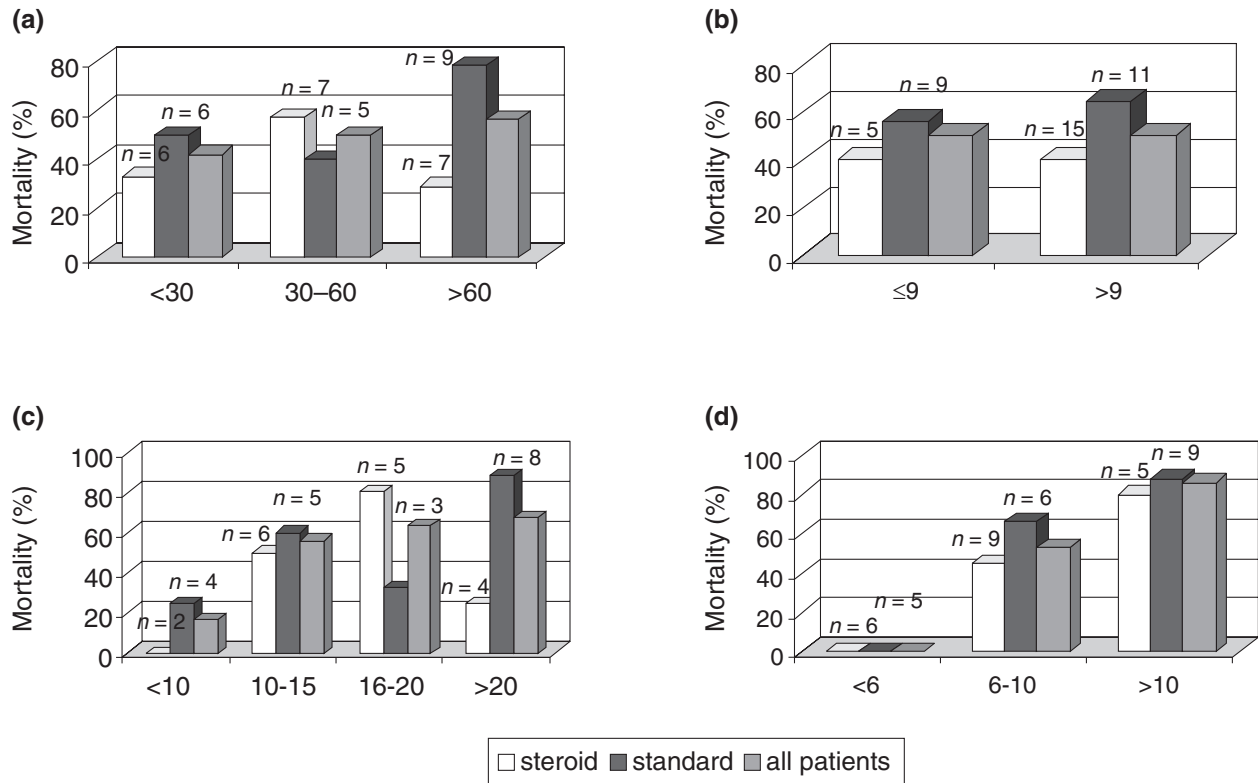
Comparison of mortality rates for **(a)** basal cortisol (μg/dl), **(b)** cortisol response to ACTH (μg/dl), **(c)** APACHE II and **(d)** maximum SOFA scores in both groups.

($P = 0.343$). The mortality rate in the patients with hospital-acquired sepsis was higher than that in the patients with community-acquired sepsis in both groups, but this difference was not statistically significant. The relationship between mortality and age, the presence of an underlying disease, vasopressor and steroid therapy, and APACHE II and SOFA scores was assessed. Age, the presence of an underlying disease, steroid therapy, basal plasma cortisol levels, and cortisol response to ACTH below 9 μg/dl were not associated with mortality. Although a univariate analysis found vasopressor therapy (OR 4.64, 95% CI 1.02–21.00), APACHE II (OR 1.18, 95% CI 1.04–1.34) and maximum SOFA (OR 1.63, 95% CI 1.23–2.16) to be effective on mortality, only the SOFA score was found related to mortality, independently of other factors (OR 2.09, 95% CI 1.01–4.30) in a multivariate analysis (Fig. 1 and Table 3).

Variations of treatment effects on the 28-day mortality among subgroups

The mortality rates among patients with a cortisol level over 60 μg/dl were 29% (2 of 7) in the steroid therapy group and 78% (7 of 9) in the standard therapy group ($\chi^2 = 3.874$, $P = 0.126$). Although there was an increase in the level of basal cortisol in patients with sepsis, 14 of 40 patients (35%)

had occult AI. The mortality rates in patients with occult AI were 40% (2 of 5) in the steroid therapy group and 55.6% (5 of 9) in the standard therapy group, respectively ($\chi^2 = 0.311$, $P = 1$). Only one patient had both basal and peak cortisol levels lower than 20 μg/dl; this patient was in the standard therapy group and died on the 7th day of treatment. This case was accepted as adrenal failure. A comparison of mortality rates for basal cortisol and cortisol responses to ACTH in both groups is shown in Figure 1. The median time to death was 5 days (95% CI 2.55–8.20) in the steroid therapy group and 5.5 days (95% CI 2.19–13) in the standard therapy group ($P = 0.496$). The reason for death in all patients was attributed to sepsis. The median stay in hospital was 14 days (95% CI 11.09–20.08) in the steroid therapy group and 13 days (95% CI 10.13–16.37) in the standard therapy group ($P = 0.406$).

Sepsis-related organ dysfunction

Organ dysfunction and failure rates of the patients on admission were 40% and 45% in the steroid therapy and the standard therapy groups, respectively (Table 4). No statistically significant difference was found between the changes in the percentage of SOFA scores of the steroid therapy group (43.1 ± 26.5%) and the standard therapy group (45.4 ± 12.7%) in survivors ($P = 0.624$).

Table 3

Average values (means ± SD) of basal cortisol, peak cortisol, cortisol responses to corticotropin, APACHE II and maximum SOFA scores according to survivors and non-survivors in both groups on the first day

Variable	Steroid therapy group			Standard therapy group		
	Non-survivors (n = 8)	Survivors (n = 12)	P	Non-survivors (n = 12)	Survivors (n = 8)	P
Basal cortisol level (µg/dl)	44.4 ± 24.8	52.5 ± 30.5	0.536	60.5 ± 34.7	40.3 ± 19.9	0.154
Peak cortisol level (µg/dl)	73.1 ± 35.1	79.2 ± 33.5	0.699	80.7 ± 45.9	60.1 ± 25.7	0.265
Cortisol response (µg/dl)	28.7 ± 22.1	21.2 ± 32.7	0.579	16.3 ± 24.6	18.2 ± 16.3	0.835
APACHE II score	17.6 ± 4.5	13.8 ± 5.8	0.130	21 ± 7.9	13.3 ± 6	0.024
Maximum SOFA score	10.6 ± 3.2	5.9 ± 3.3	0.009	11.4 ± 2.9	6 ± 3.3	0.003

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 4

Organ failure in groups at baseline

Condition	Steroid therapy group	Standard therapy group	Total
Renal failure	6 (50%)	6 (50%)	12
Liver failure	9 (52.9%)	8 (47.1%)	17
Altered mental status	10 (38.5%)	16 (61.5%)	26
DIC	5 (45.5%)	6 (54.5%)	11
Cardiac failure	0 (0%)	2 (100%)	2
Respiratory failure	2 (28.6%)	5 (71.4%)	7

DIC, disseminated intravascular coagulation.

Table 5

Average values (means ± SD) of basal cortisol, peak cortisol and cortisol responses of all patients on the first day

Variable	Steroid therapy group (n = 20)	Standard therapy group (n = 20)	P
Basal cortisol level (µg/dl)	49.3 ± 28	52.4 ± 30.8	0.737
Peak cortisol level (µg/dl)	76.8 ± 33. 3	72.5 ± 39.6	0.712
Cortisol response (µg/dl)	24.2 ± 28.5	17.1 ± 21.2	0.376

Cortisol levels and cortisol responses to ACTH

Basal and peak cortisol levels and cortisol responses to ACTH in the steroid therapy group were not significantly different from those in the standard therapy group (Table 5). The average values of basal cortisol, peak cortisol and cortisol responses to ACTH in survivors and non-survivors in both groups for the first day are shown in Table 3. There was no significant difference between the values for survivors and non-survivors. The mean basal cortisol level was 47.6 ± 26.9 µg/dl on the first day in all survivors and 17.2 ± 8.6 µg/dl on the 14th day in patients who recovered (P = 0.0003). In the steroid therapy group, the mean basal cortisol level was 52.5 ± 30.5 µg/dl on the first day and 17.6 ± 10.3 µg/dl on the 14th day (P = 0.003). In the standard therapy group, the mean basal cortisol level was 40.3 ± 19.9 µg/dl on the first day and 16.4 ± 4.6 µg/dl on the 14th day (P = 0.028) (Table 6).

Adverse events

There were no adverse effects due to steroid therapy. Only one patient, in the standard therapy group, had a secondary infection.

Discussion

Sepsis is a severe and life-threatening disease. Septic shock is associated with a mortality rate of more than 50%. Despite improvements in the overall management of such patients, including intensive fluid resuscitation, broad-spectrum antibiotic therapy, and life-support devices, mortality rates have not improved during the past decade [4]. In this randomized, double-blind study of the physiological dose of intravenous prednisolone or placebo in the treatment of sepsis, we observed an important difference in mortality rates between both groups. The mortality rates were 40% in the steroid therapy group and 60% in the standard treatment group. There was a trend towards a decrease in the mortality rate of the patients with sepsis who received physiological-dose steroid therapy. However, the differences were not statistically significant (P = 0.343). Several factors were suspected to be associated with mortality in sepsis [30,31]. Annane *et al.* [17] reported that SOFA score, high plasma cortisol levels and weak response of cortisol to ACTH were also associated with mortality. However, we found that only SOFA score was related to mortality, independently of other factors (OR 2.07, 95% CI 1.02–4.22) in the multivariate analysis.

Table 6

Comparison of basal cortisol levels (µg/dl; means ± SD) on the 1st and 14th days in recovering patients

	Steroid therapy group			Standard therapy group			Total		
	1st day	14th day	P	1st day	14th day	P	1st day	14th day	P
Cortisol	52.5 ± 30.5	17.6 ± 10.3	0.003	40.3 ± 19.9	16.4 ± 4.6	0.028	47.6 ± 26.9	17.2 ± 8.6	0.0003

Briegel *et al.* [19] showed that stress doses of hydrocortisone reduce the time for the reversal of shock, the number of organ system failures, and the length of mechanical ventilation in patients with septic shock. This finding underlines the fact that an impaired adrenocortical function contributes to vascular hyporesponsiveness in septic shock. In contrast to other studies, our study was performed in patients with sepsis, severe sepsis and septic shock with the use of physiological-dose prednisolone with or without vasopressor support. Because the administration of prednisolone does not affect the circadian adrenocortical patterns and the results of an ACTH stimulation test in adults, we preferred to use this drug [32]. In this study we did not completely evaluate the effect of the steroid on patients with vasopressor-dependent septic shock. However, in a few patients, a physiological dose of prednisolone reduces the time for the reversal of shock as defined by the cessation of vasopressor therapy.

It is known that the plasma cortisol level increases in critical illnesses and that basal cortisol levels have a positive correlation with severity of illness and prognosis. However, some investigators [16,23,33–35] showed that patients with sepsis and high baseline cortisol levels had a lower cortisol response to the ACTH stimulation test. Our entire study group had higher mean random basal and stimulated cortisol levels than those seen in outpatients. The difference between the basal cortisol levels on the 1st and 14th days in patients who recovered was statistically significant ($P < 0.0001$) (Table 5). We have also shown that basal cortisol levels correlate with the severity of the illness, and that very high cortisol levels signify a poor prognosis in the standard therapy group (Fig. 1).

Clinically significant AI is unusual in outpatients. The studies of adrenal function in critically ill patients report conflicting incidences of AI ranging from 0% to 28% [35–37]. Our results show a low incidence of AI in septic patients. One of our 40 patients had abnormal basal and peak cortisol levels (less than 20 µg/dl) and died. This condition was evaluated as AI. In the advancing process from sepsis to septic shock, we concluded that AI was not so frequent as supposed.

In recent years, several authors have proposed a syndrome of occult AI in septic shock in the presence of normal or even elevated serum cortisol concentrations. Annane *et al.* [17]

Key messages

- There was an increase in the level of basal cortisol in patients with sepsis.

- In the advancing process from sepsis to septic shock, adrenal insufficiency was not so frequent as supposed.

- Sepsis can cause occult adrenal insufficiency in the presence of normal or even elevated serum cortisol concentrations.

- Physiological-dose prednisolone therapy had a tendency towards a decrease in mortality in the patients with sepsis.

reported that 50% of patients with severe sepsis had occult AI. In the present study, 14 (35%) of the 40 patients had a subnormal cortisol response (occult AI). Five patients in the steroid treatment group had an inadequate cortisol response; two of them died. However, five of nine patients in the standard treatment group who showed inadequate cortisol response died. No statistical differences were observed in mortality rates between the patients who had occult AI ($\chi^2 = 0.311$, $P = 1$) (Fig. 1).

In conclusion, a physiological dose of intravenous prednisolone had a tendency towards a decrease in mortality in the patients with sepsis, but the difference between the two groups was not significant. Because our study had a small sample size and showed heterogeneity in population in terms of clinical severity, treatment with physiological-dose steroid in sepsis should be evaluated in a larger group of patients.

Competing interests

None declared.

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