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Low-dose hydrocortisone treatment for patients with septic shock: A pilot study comparing 3 days with 7 days

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ABSTRACT

Background and objective: **Although there is controversy regarding the benefit of low-dose corticosteroid therapy in patients with septic shock, the Surviving Sepsis Campaign has advocated that low-dose intravenous hydrocortisone be used to treat adult septic shock patients. This study investigated the effect of the duration of a stress dose of hydrocortisone on survival of septic shock patients with relative adrenal insufficiency.**

Methods: **One hundred and thirty consecutive patients who met the American College of Chest Physicians/Society of Critical Care Medicine criteria for septic shock were included in the study. An additional inclusion criterion was vasopressor support after fluid resuscitation. The primary end-point was 28-day mortality, and the secondary end-points were shock reversal and mortality in the intensive care unit and hospital. All eligible patients were prospectively randomized to receive hydrocortisone treatment for 3 or 7 days. Hydrocortisone treatment was started at a dose of 50 mg every 6 h.**

Results: **Baseline data at recruitment did not differ between the two groups. After 28 days, mortality did not differ between the 3- and 7-day treatment groups (33.8% vs 36.9%, $P = 0.629$). Mortality rates in the intensive care unit and hospital did not differ significantly between the two groups. The median time to withdrawal of vasopressor therapy was 5.0 days in the 3-day treatment group and 6.4 days in the 7-day treatment group ($P = 0.102$).**

Conclusions: **This pilot study showed that in patients with septic shock and relative adrenal insufficiency, 28-day mortality did not differ between those treated with low-dose hydrocortisone for 3 or 7 days.**

SUMMARY AT A GLANCE

Although the Surviving Sepsis Campaign has advocated low-dose hydrocortisone treatment for septic shock patients showing poor response to fluid resuscitation and vasopressors, the optimum duration of therapy remains uncertain. This pilot study showed no difference in 28-day mortality between those treated with corticosteroids for 3 or 7 days.

Key words: adrenal insufficiency, hydrocortisone, mortality, septic shock, shock reversal.

INTRODUCTION

Septic shock remains an important cause of mortality and morbidity in intensive care units (ICUs).[1–3] During sepsis, the systemic inflammatory response compromises reciprocal communication between the neuroendocrine and peripheral immune systems.[4] The various drugs developed against specific targets of the cytokine cascade have not been shown to improve patient survival.[5,6] Trials of glucocorticoid treatment in patients with sepsis have been based on the fundamental role of glucocorticoids in the stress response to infection, and increasing knowledge about the anti-inflammatory and immunosuppressive pharmacodynamic profiles of glucocorticoids. Although individual responses to infection are determined by many factors, including the virulence of the infective agent causing sepsis, patient comorbidities and management, the initial immune response is hyper-inflammatory but progresses rapidly to being hypo-inflammatory.[7] During this hypo-inflammatory state, anti-inflammatory treatment may prolong depression of immune function, culminating in death.

A randomized trial showed that 7 days of treatment with low-dose glucocorticoid reduced the risk of death in patients with septic shock and relative

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adrenal insufficiency.[8] However, recent systematic reviews have suggested that the effect of corticosteroid therapy on survival of patients with septic shock is debatable,[9–11] and more recent larger studies have not shown significant effects.[12] Although there is controversy regarding the benefit of low-dose corticosteroid therapy in patients with septic shock, one consistent finding is that there is an accelerated reversal of shock.[12–14] Therefore, the Surviving Sepsis Campaign has advocated that low-dose intravenous hydrocortisone be used to treat adult septic shock patients only after it has been determined that blood pressure is responding poorly to fluid resuscitation and vasopressor therapy.[15] The optimum duration of corticosteroid therapy remains uncertain.[8,12–14]

We hypothesize that if rapid reversal of shock is a major benefit of low-dose corticosteroid therapy, then short courses of these drugs could be used to this end. Briegel *et al.* reported that the median duration of vasopressor support was 2 days in a group of patients treated with corticosteroids,[13] whereas Oppert *et al.* showed that the time to cessation of such support was 2.2 days in corticosteroid-treated patients.[14] In this study, we investigated the difference in mortality between patients with septic shock and relative adrenal insufficiency, who received low-dose glucocorticoid treatment for either 3 or 7 days. The effects of the two durations of treatment on reversal of shock were also compared.

METHODS

Study population

Between March 2004 and December 2006, 234 patients, who were 18 years of age or older, were prospectively screened to determine whether they met the criteria for septic shock. The diagnosis of septic shock was based on the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus definitions for sepsis, severe sepsis and septic shock:[16] (i) evidence of infection; (ii) evidence of a systemic response to infection; (iii) systolic blood pressure <90 mm Hg despite adequate fluid resuscitation; and (iv) hypoperfusion or organ dysfunction attributable to sepsis.

The inclusion criteria were onset of septic shock within 6 h and relative adrenal insufficiency, defined as an increase in cortisol level of <9 μg/dL or a basal cortisol level of <25 μg/dL.[8,17,18] Exclusion criteria included advanced cancer, immunosuppression, previous treatment with corticosteroids, refusal of the attending staff or patient family and absence of adrenal insufficiency. Altogether 130 patients with relative adrenal insufficiency were randomized to receive either 3 or 7 days of treatment, after a short corticotropin test was performed (Fig. 1). The study was approved by the Ethics Committee of Asan Medical Center in Korea and written informed consent was obtained from all patients or their relatives.

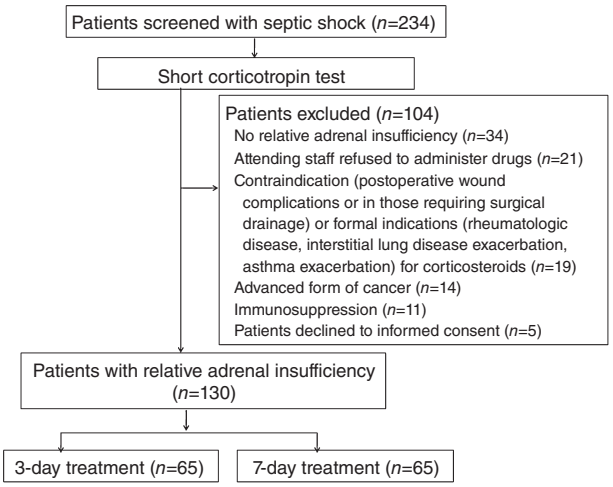

Figure 1 Flow chart showing the inclusion and exclusion criteria for screening of patients with septic shock.

Randomization

The randomization of patients (in a 1 : 1 ratio) was stratified according to a table of random sampling numbers. The sequence was concealed from investigators and treating physicians. However, medical and nursing staff were aware of the study group assignments because the duration of treatment differed between the two groups. At the end of the study, clinical evaluations were performed by a staff member who was unaware of the study group assignments and the appropriateness of treatment.

Treatment

Patients were treated with standard therapy for septic shock, according to international guidelines:[15] administration of antibiotics and vasoactive drugs, with fluid replacement and mechanical ventilatory support. Patients were enrolled within 6 h of the diagnosis of septic shock, and adrenocorticotropic hormone (ACTH) stimulation tests were performed. Hydrocortisone was administered intravenously every 6 h as a 50 mg bolus, while awaiting the results of cortisol measurements. Patients with relative adrenal insufficiency were randomized to 3 or 7 days of corticosteroid therapy.

Definitions

Reversal of shock was defined as the maintenance of a mean blood pressure >65 mm Hg for ≥1 h, after the cessation of vasopressor support (noradrenaline at any dose, dopamine ≥5 μg/kg/min).[13,14] Superinfection was defined as a new infection occurring 48 h or more after the initiation of treatment with a study drug.[19] Failure of major organ systems was defined as a Sequential Organ Failure Assessment (SOFA) score of 4 points.[20]

Data collected at enrolment

General characteristics and severity of illness, as assessed by acute physiology and chronic health evaluation II (APACHE II) and SOFA scores,[20] were recorded. Haematological and biochemical data and arterial lactate levels were measured, and blood culture and culture of specimens from the site of infection were routinely performed. Cortisol levels were measured using a radioimmunoassay kit (Siemens Diagnostics, Los Angeles, CA, USA). The short corticotropin test was performed with a 250 μg intravenous bolus of ACTH (Synacthen; Novartis, Basel, Switzerland). Cortisol levels were measured at baseline, and 30 and 60 min after the injection of 250 μg of ACTH.

End-points

The primary end-point was 28-day mortality in septic shock patients with relative adrenal insufficiency. The secondary end-points were the reversal of shock, and death rates and duration of stay in the ICU and hospital.

Statistical methods

A sample size of 272 patients (136 per group) was required to achieve a statistical power of 80% to detect a relative risk of 1.5 for 28-day mortality, based on the current death rate of 35% for patients with septic shock at Asan Medical Center. A maximum overall two-sided probability of a type I error of 5% was accepted.

Data were analysed according to the intention-to-treat principle. Categorical data were compared using chi-square tests, and continuous data were evaluated using Student's *t*-tests. Kaplan–Meier curves for cumulative survival during the 28-day observation period were constructed, and compared using the log–rank test. Cumulative event curves for time-to-vasopressor, which was a competing cause of death, were calculated and compared using Gray's method.[21] Continuous variables are expressed as mean ± SD, and a two-tailed P value <0.05 was considered significant. SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and the R programming language with cmprsk library were used for statistical analyses.

RESULTS

Characteristics of the study patients at enrolment

Between March 2004 and December 2006, 164 patients were enrolled in the study (Table 1). One hundred and thirty patients were finally randomized to the two groups, according to the presence of adrenal insufficiency (65 each in the 3- and 7-day treatment groups). At baseline, there were no differences between the groups with respect to general characteristics, severity of illness (Table 2) or laboratory data (Table 3). The response to corticotropin and the type and site of infection were similar in the two groups. The incidence of ARDS (13.8% in the 3-day treatment group vs 20.3% in the 7-day treatment group, $P = 0.358$) and renal replacement (35.4% vs 35.3%, $P = 0.470$) were also similar in the two groups.

Initial management of shock was similar in the two study groups (Table 4). Hydrocortisone was administered intravenously to all patients within 24 h of randomization. Forty-three patients in the 3-day treatment group (66.2%) and 38 patients in the 7-day treatment group (58.5%) received corticosteroids within 6 h of the onset of septic shock ($P > 0.05$). Four patients in the 3-day treatment group (6.2%) and six patients in the 7-day treatment group (9.2%) received prolonged corticosteroid treatment for ARDS, acute exacerbation of interstitial lung disease, adrenal

Table 1 Clinical characteristics of the 164 patients with relative or no adrenal insufficiency

	Patients with relative adrenal insufficiency ($n = 130$)	Patients with no adrenal insufficiency ($n = 34$)	P value
Age, years	62.1 ± 12.8	65.3 ± 13.4	0.203
Gender, men : women	83 : 47	22 : 12	0.926
APACHE II score	29.3 ± 8.5	25.9 ± 7.6	0.081
SOFA score	12.8 ± 3.5	10.8 ± 3.3	0.022
Mixed venous blood saturation, %	69.2 ± 12.2	65.1 ± 12.2	0.255
ACTH concentration, μg/dL	67.5 ± 14.9	33.8 ± 29.9	0.038
Cortisol concentration, μg/dL			
Before corticotropin test	26.9 ± 2.0	40.5 ± 14.2	0.001
30 min after corticotropin test	34.3 ± 27.0	58.2 ± 28.9	<0.0001
60 min after corticotropin test	32.1 ± 20.3	65.5 ± 33.7	<0.0001
28-day mortality, *n* (%)	46 (35.4)	12 (35.3)	0.992

Values are mean ± SD unless otherwise indicated.

ACTH, adrenocorticotropic hormone; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 2 Demographic and clinical characteristics of the 130 patients who were randomized to 3 or 7 days of corticosteroid treatment

	3 days of treatment ($n = 65$)	7 days of treatment ($n = 65$)	*P* value
Age, years	61.3 ± 12.5	62.9 ± 13.2	0.479
Gender, men : women	43 : 22	40 : 25	0.358
Prior or pre-existing disease, *n* (%)			0.369
Chronic lung disease	6 (9.2)	7 (10.8)	
Chronic liver disease	8 (12.3)	8 (12.3)	
Chronic renal disease		1 (1.5)	
Congestive heart disease	5 (7.7)	2 (3.1)	
Diabetes	1 (1.5)	2 (3.1)	
Malignancy	18 (27.7)	24 (36.9)	
Neurological disease	9 (13.9)	6 (9.3)	
Other	10 (15.3)	4 (6.1)	
None	8 (12.3)	11 (16.9)	
Admission category, *n* (%)			>0.999
Medical	60 (92.3)	59 (90.8)	
Elective surgery	4 (6.2)	6 (9.2)	
Emergency surgery	1 (1.5)		
APACHE II score	29.0 ± 9.1	29.6 ± 7.8	0.648
SOFA score	12.8 ± 3.5	12.6 ± 3.5	0.109
Type of infection, *n* (%)			0.342
Community-acquired	48 (73.8)	42 (64.6)	
Hospital-acquired	17 (26.2)	23 (35.4)	
Site of infection, *n* (%)			0.790
Pneumonia	25 (38.5)	33 (50.8)	
Intra-abdominal	3 (4.6)	4 (6.1)	
Urinary tract infection	10 (15.4)	2 (3.1)	
Bacteraemia	7 (10.8)	6 (9.2)	
Biliary tract	9 (13.8)	4 (6.2)	
Other	5 (7.7)	6 (9.1)	
Unknown	6 (9.2)	10 (15.4)	
Positive culture, *n* (%)			0.670
Gram-positive	15 (23.1)	13 (20.0)	
Gram-negative	26 (40.0)	22 (33.8)	
Other[†]	7 (10.6)	6 (9.1)	
Culture not obtained	17 (26.2)	24 (36.9)	

[†] Anaerobe, fungus, mixed, Rickettsia, virus.
Values are mean ± SD unless otherwise indicated.
APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

insufficiency, bronchospasm or oedema of the brain, after enrolment in the study.

Mortality

The overall 28-day mortality was 35.4%. By day 28, 22 patients (33.8%) in the 3-day treatment group and 24 (36.9%) in the 7-day treatment group had died (risk ratio (RR) 1.00, 95% CI: 0.487–2.052). The 28-day mortality did not differ significantly between patients with septic shock and relative adrenal insufficiency who received hydrocortisone for 3 or 7 days (primary outcome) (Fig. 2).

Mortality rates also did not differ between the study groups at any other time (Table 5). In a subgroup analysis that excluded 10 patients who received prolonged corticosteroid therapy, the primary and secondary outcomes did not differ between the treatment groups (Fig. S1 and Table S1 in the online supporting information). The most frequent cause of death in both groups was septic shock with multiorgan failure.

Reversal of shock

The proportion of patients with reversal of shock was similar in the two groups; 42 of 65 in the 3-day treatment group (65%, 95% CI: 53–77) and 41 of 65 in the 7-day treatment group (63%, 95% CI: 51–75). Forty-eight of the 65 patients in the 3-day treatment group (74%, 95% CI: 63–85) and 45 of 65 in the 7-day treatment group (71%, 95% CI: 59–82) showed haemodynamic stability at least 24 h after the cessation of vasopressor treatment. The median time to

Table 3 Baseline clinical and laboratory measurements for the patients who received 3 or 7 days of corticosteroid treatment

	3 days of treatment ($n = 65$)	7 days of treatment ($n = 65$)	*P* value
Mixed venous blood saturation, %	67.3 ± 10.6	70.8 ± 13.3	0.170
ESR, mm/h	40.4 ± 36.6	44.7 ± 39.7	0.626
Haemoglobin, g/L	110 ± 28	102 ± 22	0.064
Leukocytes, $\times 10^9$/L	1.176 ± 9.249	1.246 ± 9.658	0.678
Platelets, $\times 10^9$/L	140.9 ± 102.1	154.3 ± 129.3	0.520
Arterial lactate, mmol/L	5.5 ± 3.7	5.1 ± 4.1	0.539
Arterial lactate, after cessation of glucocorticoid therapy, mmol/L	3.6 ± 2.6	3.5 ± 3.3	0.866
BNP, pg/mL	662.0 ± 1106.4	614.2 ± 1035.3	0.807
C-reactive protein, mg/L	163 ± 116	170 ± 102	0.712
Albumin, mg/L	23 ± 6	22 ± 6	0.424
ACTH concentration, μg/dL	62.4 ± 92.7	71.8 ± 173.2	0.743
Cortisol concentration, μg/dL			
Before corticotropin test	26.3 ± 17.0	27.5 ± 28.3	0.762
30 min after corticotropin test	30.8 ± 17.7	37.2 ± 32.9	0.252
60 min after corticotropin test	31.3 ± 15.7	32.8 ± 24.2	0.687
Time from randomization to corticosteroid treatment, h	6.3 ± 2.8	7.5 ± 2.3	0.757
Time from onset of shock to vasopressor therapy, h	4.6 ± 6.9	6.2 ± 6.1	0.105
Time from onset of shock to corticosteroid treatment, h	6.3 ± 15.5	6.4 ± 11.9	0.495

Values are mean ± SD unless otherwise indicated.
ACTH, adrenocorticotropic hormone; BNP, brain natriuretic peptide.

Table 4 Management of shock over the initial 24 h in 130 patients who received 3 or 7 days of corticosteroid treatment

Variable	3 days of treatment ($n = 65$)	7 days of treatment ($n = 65$)	*P* value
Fluid therapy			
Initial 6 h, mL	3233.4 ± 1887.0	3065.3 ± 1645.9	0.592
Initial 24 h, mL	6855.4 ± 3024.1	6455.4 ± 2957.0	0.451
Type and maximum dose of vasopressor			
Dopamine, *n* (%)	41 (63)	49 (75)	
Initial 6 h, μg/kg/min	9.0 ± 8.3	10.2 ± 8.1	0.399
Initial 24 h, μg/kg/min	6.0 ± 8.0	8.4 ± 8.1	0.095
Noradrenaline, *n* (%)	47 (72)	41 (63)	
Initial 6 h, μg/kg/min	11.7 ± 25.8	17.3 ± 37.4	0.338
Initial 24 h, μg/kg/min	33.4 ± 50.0	32.1 ± 49.1	0.886
Ventilator support, *n* (%)	52 (80.0)	58 (89.2)	0.112
Use of etomidate, *n* (%)	11 (16.9)	8 (12.3)	0.456
Duration of corticosteroid therapy, days	3.0 ± 0.9	7.3 ± 3.3	<0.001
Duration of antibiotic therapy, days	21.1 ± 16.6	18.2 ± 12.3	0.266
Appropriateness of antibiotic therapy, %	71.4	70.0	0.533

Values are mean ± SD unless otherwise indicated.

withdrawal of vasopressor therapy was 5.0 days in the 3-day treatment group and 6.4 days in the 7-day treatment group ($P = 0.102$). The time to withdrawal of vasopressor therapy did not differ between the two groups (Fig. 3). Seven patients in the 3-day treatment group and 10 patients in the 7-day treatment group showed recurrent hypotension after completion of the course of treatment.

Adverse events

The rate of secondary infection did not differ between the groups (RR 1.131, 95% CI: 0.427–2.997; $P = 0.804$). Blood glucose levels did not differ between the treatment groups; slightly higher doses of insulin were administered to the 3-day treatment group, but the difference between the groups was not significant (RR 0.999, 95% CI: 0.999–1.000; $P = 0.139$) (Table S2 in the online supporting information).

DISCUSSION

There was no significant difference in 28-day mortality between patients with septic shock and relative adrenal insufficiency, who received 3 or 7 days of

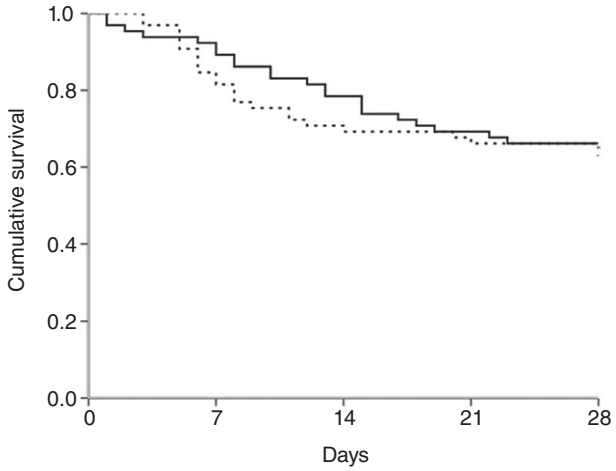

Figure 2 Kaplan–Meier curve showing the probability of survival in patients with septic shock. (——) 3-day treatment; (·····) 7-day treatment. Log–rank test: *P* value = 0.629.

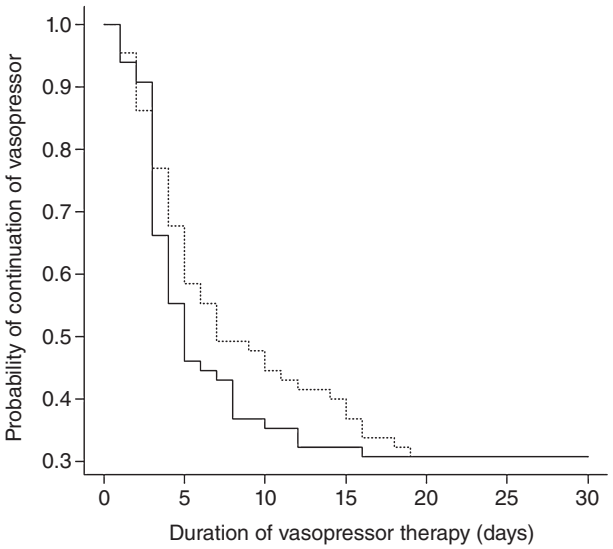

Figure 3 Distribution of time to withdrawal of vasopressor therapy in patients with septic shock who received three days or seven days of corticosteroid treatment. (——) 3-day treatment; (·····) 7-day treatment. Gray's test: *P* value = 0.621; Log–rank test: *P* value = 0.656.

Table 5 The clinical course in 130 patients with relative adrenal insufficiency who received 3 or 7 days of corticosteroid treatment

Variable	3 days of treatment (*n* = 65)	7 days of treatment (*n* = 65)	*P* value
28-day mortality, *n* (%)	22 (33.8)	24 (36.9)	0.714
ICU mortality, *n* (%)	21 (32.3)	24 (36.9)	0.713
Hospital mortality, *n* (%)	23 (35.4)	27 (41.5)	0.589
Shock-free period, days	19.6 ± 21.6	16.7 ± 18.7	0.422
Use of ventilator, days	9.8 ± 12.1	9.4 ± 8.0	0.827
ICU stay, days	11.0 ± 13.4	13.2 ± 11.8	0.326
Hospital stay, days	31.7 ± 29.5	30.3 ± 23.7	0.778
Cause of mortality, *n* (%)			0.366
Septic shock	17 (77.3)	14 (58.3)	
Respiratory failure	2 (9.1)	8 (33.3)	
Myocardial infarction	1 (4.5)		
Brain death	1 (4.5)	2 (8.3)	
Liver failure	1 (4.5)		

Values are mean ± SD unless otherwise indicated.
ICU, intensive care unit.

replacement therapy with low-dose hydrocortisone. Mortality in the ICU or hospital, duration of vasopressor therapy and the proportion of patients experiencing reversal of shock did not differ significantly between the two groups.

These results indicate that clinicians treating patients with septic shock and relative adrenal insufficiency should consider a short course of therapy for patients who achieve haemodynamic stability after 3 days of low-dose corticosteroid therapy. There are several advantages associated with a short course of corticosteroid therapy. First, reversal of shock in patients with severe septic shock is the principal rationale for a short course of corticosteroid therapy. International guidelines for the management of septic shock suggest that intravenous hydrocortisone should be administered to adult patients with septic shock only after it has been determined that blood pressure has responded poorly to fluid resuscitation and vasopressor therapy.[22] In previous studies, reversal of shock usually occurred within 3 days, and did not require 7 days of treatment.[13,14] Briegel *et al.* reported a median duration of vasopressor support of 2 days, whereas Oppert *et al.* reported that the time to cessation of vasopressor support was 2.2 days in corticosteroid-treated patients. The CORTICUS study showed that hydrocortisone hastened the reversal of shock in patients who responded to corticotropin.[12]

The main benefit of low doses of corticosteroid in patients with septic shock may be due to an increase in vasomotor tone rather than an anti-inflammatory action.[23,24] Second, no study has compared the responses to tapering or abrupt cessation of corticosteroid therapy, which is an important factor affecting the duration of corticosteroid treatment. As in the study of Annane *et al.*,[8] corticosteroid treatment was stopped abruptly after 3 or 7 days. Keh *et al.* reported that six of 20 (30%) patients required further vasopressor therapy after the abrupt cessation of corticosteroids,[25] whereas the present study showed that 7/65 (11%) and 10/65 (15%) patients needed such treatment after 3 and 7 days of corticosteroid therapy, respectively. Third, it has been suggested that any gain from an early reversal of shock is counterbalanced by the later development of complications.[26] In the CORTICUS study, tapering of corticosteroid therapy between day 5 and day 11 increased the incidence of superinfection, including new episodes of sepsis or septic shock, in the hydrocortisone-treated group.[12] This might be attributable to the longer duration of corticosteroid use. Several randomized controlled trials have shown unequivocally that short-term administration of high doses of glucocorticoids is ineffective or even harmful in patients with early septic shock, most probably because of immunosuppression and an increased incidence of secondary infections.[5,27–29]

Time-sensitive care is critical in patients with septic shock,[30] and in studies assessing the treatment of such patients, the timing of enrolment is important. Annane *et al.* enrolled patients within 8 h of the development of symptoms,[8] whereas the CORTICUS study enrolled patients at 72 h,[12] the early goal-directed therapy study enrolled patients within 1 h,[30] and patients were enrolled within 6 h in the present study.

This study had some limitations. This single-centre study with a small sample size may have underestimated the significance of the clinical outcomes, and large randomized, double-blinded multicentre studies are required to confirm the findings. This study was terminated early because of a poor rate of enrolment towards the end of the study. Second, randomization was performed in an unblinded fashion. Because a dummy infusion was not performed in patients receiving 3 days of therapy, the medical and nursing staff were aware of the study group assignments. Third, there was no protocol for tapering vasopressor therapy because this was determined by the attending clinicians. This might have resulted in delayed tapering of vasopressor therapy. Finally, the definition of relative adrenal insufficiency that was used may have been inaccurate, because the current recommendation is that adrenal insufficiency in critically ill patients is best defined as a delta total serum cortisol concentration <9 μg/dL after administration of ACTH (250 μg), or a random total cortisol concentration of <10 μg/dL.[31] However, the primary outcome did not differ when the groups were re-categorized according to a baseline cortisol cut-off level of <10 μg/dL (log–rank *P* value 0.843). Although the short corticotropin test has not been advocated for assessing the advisability of corticosteroid treatment in patients with septic shock,[11,22] the patients without adrenal insufficiency showed low SOFA scores and similar mortality as compared with those with adrenal insufficiency.

In summary, this pilot study showed no difference in 28-day mortality or reversal of shock in patients with septic shock and relative adrenal insufficiency, who received 3 or 7 days of therapy with low-dose hydrocortisone. A large randomized multicentre study will be required to confirm these findings.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Figure S1 Kaplan–Meier analysis of the probability of survival in subgroup analysis. The probability of survival did not differ significantly between patients with septic shock who received hydrocortisone for 3 days (solid line) and those who received hydrocortisone for 7 days (dotted line).
Table S1 Clinical courses in subgroup analysis.
Table S2 Blood glucose level and amount of insulin in 130 patients with relative adrenal insufficiency.

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