Adrenal insufficiency and its prognosis of septic shock patients in intensive care unit

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Adrenal insufficiency and its prognosis of septic shock patients in intensive care unit

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The Master's Thesis submitted to the

Department of Medicine

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the

degree of Master of Medical Science

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June, 2008

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June, 2008

ACKNOWLEDGEMENTS

This page is exclusively designed to note my gratitude and respect for those who helped me to complete my thesis. I am deeply indebted to my supervisor Prof. Dr. Joon Chang for his kind help, guidance, support and encouragement throughout my study. This study would not have been possible without his assistance and cooperation. Sincere gratitude goes out to my reviewers, Prof. Dr. Shin Ok Koh and Prof. Dr. Se Kyu Kim who had the patience and fortitude to read my thesis and provided constructive criticism to help me defend it. Their guidance not only improved my dissertation but also will benefit my future work. I would like to express my sincere gratitude to Prof. Dr. Young Sam Kim for his valuable hints, assistance on statistical analysis, and offering suggestions for improvement. I also sincerely thank my colleagues, Ji Young Son, Soo Jung Hong, You Jung Ha, Soo Hyun Lee, Kyung Min Kim and Min Kyu Jung for their supports. Finally, my parents are the ones to whom my special gratitude and respect go to. They are the ones who withstood my being away from them, the ones who always used to strengthen my will to achieve my ambition.

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ABSTRACT

Adrenal insufficiency and its prognosis of septic shock patients

in intensive care unit

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Backgrounds: Since the relationship between sepsis and relative adrenal insufficiency has been reported, short corticotropin stimulation tests have been performed to identify relative adrenal insufficiency and determine to whom corticosteroid should be administered. The objective of this study was to evaluate the efficacy of corticosteroid therapy in a broad population of septic shock patients with and without relative adrenal insufficiency.

Patients and Methods: A retrospective study was conducted in an intensive care unit at Severance Hospital in Seoul, Republic of Korea, between June 2005 and December 2007. The study included 103 critically ill patients who underwent a short corticotropin test because

of prolonged septic shock.

Results: Among 103 patients, 36 (34.9%; 22 in the corticosteroid group and 14 in the conservative group) showed relative adrenal insufficiency and 67 (65.1%; 20 in the corticosteroid group and 47 in the conservative group) did not. At day 28, there was no significant difference in mortality between the corticosteroid and conservative groups (36% vs. 29%; p=0.63) in patients with relative adrenal insufficiency. There was also no significant difference in mortality between the 2 treatment groups (15% vs. 30%; p=0.20) in patients without relative adrenal insufficiency. Basal serum cortisol was significantly higher in non-survivors than in survivors (24.0±13.2 ㎍/㎗ vs. 18.1±12.4 ㎍/㎗; p=0.04) and was also significantly elevated in patients with relative adrenal insufficiency than those without (24.9±16.8 ㎍/㎗ vs. 17.1±9.1 ㎍/㎗; p<0.01).

Conclusions: Corticosteroid did not improve survival of septic shock patients regardless of relative adrenal insufficiency. Therefore, short corticotropin stimulation tests would not be helpful in identifying patients to be given corticosteroid. In addition, basal serum cortisol was not only a significant predictor of mortality but also of response to short corticotropin stimulation tests.

Key Words : Adrenal insufficiency, Corticosteroid, Septic shock

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I. INTRODUCTION

Septic shock has been recognized as a major problem in critically ill patients because of its high mortality rate.[1] Even though antibiotic therapies and other intensive care methods have improved steadily during the past decade, mortality from septic shock still remains close to 50%.[2] Therefore, interest in developing new pharmacologic agents including corticosteroid has been stimulated to reduce morbidity and mortality of patients with septic shock. Therapeutic use of corticosteroid in patients with sepsis was first studied by Perla and Marmorston in 1940.[3]

In the early days, corticosteroid was used for its anti-inflammatory effects. Corticosteroid affects immune-mediated inflammatory reactions in several ways. First of all, it influences the circulation of leukocytes and inhibits many

functions of leukocytes and immune accessory cells. Corticosteroid suppresses immune activation of these cells, inhibits production of cytokines and other mediators of inflammation, and causes resistance to cytokines. It also suppresses the function of type 1 helper T-lymphocytes and stimulates apoptosis of eosinophils. Moreover, it inhibits expression of adhesion molecules and their corresponding receptors and potentiates the acute phase reaction. Suppression of the phospholipase A_2, cyclooxygenase$_2$, and nitric oxide synthase$_2$ genes also decreases production of prostanoids, platelet-activating factors, and nitric oxide.[4-7] However, many conflicting studies on the efficacy of corticosteroid in specific infection, severe infection, and septic shock have been reported. After reviewing 32 studies of corticosteroid therapy for bacterial infection, Weitzman and Berger pointed out the inappropriate methodology of the studies.[8] In 1976, Schumer et al. reported a reduction in mortality rate of septic shock patients treated with a high dose of corticosteroid (dexamethasone 3 mg/kg or methylprednisolone 30 mg/kg) in prospective and randomized study.[9] Their results motivated further investigation and aroused criticism. In the 1980s, several large multicenter studies reported that there was no benefit in reducing mortality from treating sepsis or septic shock patients with corticosteroid,[2, 10, 11] and the use of corticosteroid for anti-inflammatory purposes in patients with severe sepsis or septic shock was tempered.

However, in the 1990s, more efforts to better characterize septic patients with the worst outcome were kept and the association between severe sepsis

and relative adrenal insufficiency was observed.[12, 13] These results stirred new interest in corticosteroid replacement therapy with a low dose of corticosteroid for longer periods.[14] In 2002, Annane et al. reported increased survival and decreased need for vasopressors in patients with septic shock and relative adrenal insufficiency by using a low dose of hydrocortisone and fludrocortisone.[15] However, controversy surrounding the physiologic dose of corticosteroid remained and its benefits to patients with septic shock and relative adrenal insufficiency remained unproven.

Recently, Sprung et al. and Annane et al. published a multicenter, randomized, double-blind, placebo-controlled study of steroid treatment in patients with septic shock which showed that survival was not increased even in patients unresponsive to corticotropin stimulation tests (defined as relative adrenal insufficiency) but reversal of shock was seen faster in patients in whom shock was reversed.[16] The “Surviving Sepsis Campaign 2008” recommended hydrocortisone treatment in adult septic shock poorly responsive to fluid resuscitation and vasopressor therapy. However, it suggested corticotropin stimulation tests should not be used to determine which patients with septic shock would receive hydrocortisone.[17]

In Korea, there have been 2 previous reports on serum cortisol in patients with sepsis or septic shock. Lee et al. reported that both serum cortisol and 24-hour urinary cortisol were significant prognostic factors in sepsis and that they showed strong correlation with other parameters.[18] Kwon et al. stated that even though basal serum cortisol level was not predictive of response to

corticotropin stimulation tests, it was a significant prognostic factor in patients with septic shock. They also stated that there was no benefit of corticosteroid use in patients with septic shock and relative adrenal insufficiency.[19]

The objective of this study was to evaluate the efficacy of low-dose hydrocortisone therapy in a broad population of patients with septic shock who did and did not have a response to corticotropin tests.

II. MATERIALS AND METHODS

1. Study Population

A total of 132 patients who underwent a short corticotropin stimulation test in an intensive care unit at Severance Hospital in Seoul, Republic of Korea, between June 2005 and December 2007 were retrospectively enrolled in the study if they were 18 yr of age or older and had septic shock with the need for vasopressors. Patients were excluded if they were younger than 18 yr old, pregnant, had evidence of acute myocardial infarction, pulmonary embolism, an advanced form of cancer, or acquired immunodeficiency syndrome (AIDS) infection. Moreover, patients taking corticosteroid, etomidate, ketoconazole, or any other drugs known to influence the hypothalamus-pituitary-adrenal axis, were excluded.

2. Definitions

Septic shock was defined as sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 hr despite adequate fluid resuscitation or as needed for vasopressors to maintain systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg. Sepsis was defined as systemic inflammatory response syndrome (SIRS) with proven or suspected microbial etiology. SIRS was defined as the presence of microbes or their toxins in blood or 2 or more of the following conditions (noninfectious etiology): (1) body temperature

>38℃ or <36℃; (2) leukocytosis (>10,000/㎕) or leukopenia (<4,000/㎕) or >10% bands; (3) heart rate >90 beats/min; and (4) respiratory rate >24 breaths/min.[20] Relative adrenal insufficiency (RAI) was diagnosed when the difference between T0 and the highest of value of T30 or T60 was no more than 9 ㎍/dL.[12, 13, 15, 16]

3. Study Methods

A. Data Collection

Patients' clinical and laboratory data were recorded with retrospective chart review. Clinical evaluation included general characteristics of patients such as demographic data, diagnosis, acquisition of infection, infection site, and severity of disease. Severity of disease was assessed by acute physiology and chronic health evaluation (APACHE) II, simplified acute physiology score (SAPS), sequential organ failure assessment (SOFA) score, and vital signs (body temperature, systolic blood pressure, heart rate, etc.). Laboratory variables included culture of blood and other potential sites of infection, hematology and blood chemistry data, and blood gas determinations. Blood samples were taken immediately before (T0), 30 (T30) and 60 (T60) min after short corticotropin stimulation test. Tetracosactrin (Synacthen®) was used for short corticotropin stimulation tests and serum cortisol level was measured using chemoluminescence immunoassay. For high-dose and low-dose short corticotropin stimulation tests, 250 ㎍ and 1 ㎍ of tetracosactrin were used, respectively.

B. Statistical Analysis

Statistical analysis was conducted using SPSS 12 (SPSS, Chicago, IL, USA). Analysis was performed on patients with relative adrenal insufficiency (non-responders to corticotropin stimulation test), without relative adrenal insufficiency (responders to corticotropin stimulation test), and all patients. Pretreatment characteristics were compared between groups using *t* test or Mann-Whitney U test (for continuous variables) and χ^2 or Fisher's exact test (for categorical variables) when appropriate. Outcomes were assessed by Kaplan-Meier method and compared between groups using log-rank test. A Cox proportional hazards regression model was used to estimate hazard ratio of variables related to 28-day mortality. Multivariate analysis was performed using a logistic regression model with enter method to estimate the odds ratio of relative adrenal insufficiency (95% confidence intervals, CI). For all tests, $p<0.05$ was considered statistically significant.

III. RESULTS

1. Study Description

From June 2005 to December 2007, 132 patients were eligible for the study and two different types of corticotropin stimulation tests (high-dose or low-dose) were used during the period. Assuming that patients who showed response to low-dose corticotropin stimulation tests would also show response to high-dose corticotropin stimulation tests, responders to low-dose corticotropin stimulation tests were regrouped into responders as patients with adrenal insufficiency (Figure 1). As a result, 29 patients who were non-responders to low-dose corticotropin stimulation tests were excluded and a total of 103 patients were finally enrolled in this study.

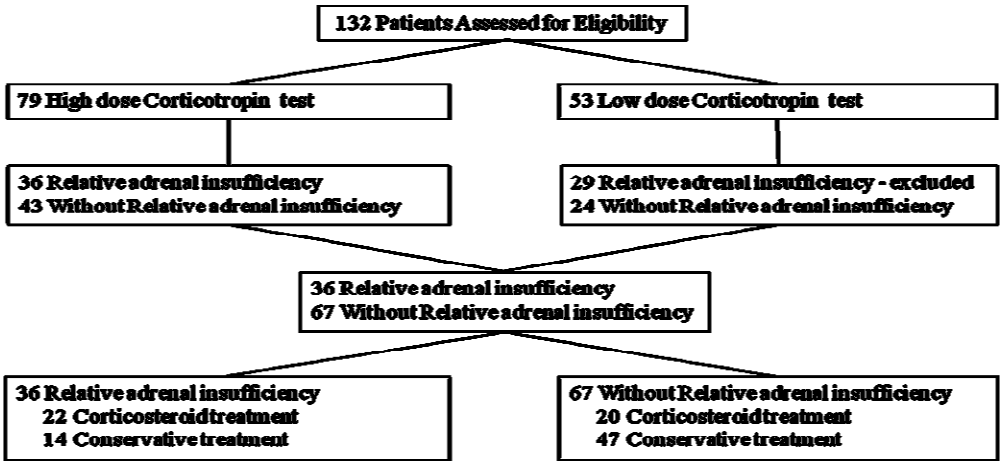

Figure 1. Study Population

2. Characteristics of Study Patients at Inclusion

Among the 103 patients in this study, 36 (34.9%) had relative adrenal insufficiency (corticosteroid, 22; conservative, 14) and 67 (65.1%) did not (corticosteroid, 20; conservative, 47). Demographic characteristics, diagnosis, acquisition of infection, and infection site are shown in Table 1. Patients' previous diseases included mostly cardiovascular (41; 39.8%) and endocrinological (39; 37.9%) diseases, and reason for hospital admission was community-acquired infection of medical problems for the most part. The lung was the main source of infection (66; 64.1%).

At baseline, the 2 groups showed balanced clinical characteristics including vital signs, severity of disease, and relative adrenal insufficiency related measures (Table 2). Despite no statistical significance, means of APACHE II, SAPS, and SOFA scores were all higher in the conservative treatment group than the corticosteroid treatment group. There were 92 mechanically ventilated patients (89.3%) and the rates were higher in the corticosteroid group (95.0%) than conservative treatment group (85.0%) statistical significance.

Baseline serum cortisol was similar in the corticosteroid and conservative treatment groups in patients with relative adrenal insufficiency (24.4±18.8 ㎍/㎗ vs. 25.7±13.8 ㎍/㎗; p=0.53) and also was similar in 2 treatment groups of all patients (19.3±15.0 ㎍/㎗ vs. 20.2±11.2 ㎍/㎗; p=0.72). However, it was higher in the corticosteroid treatment group than in the conservative treatment group without relative adrenal insufficiency (13.6±5.7

㎍/㎗ vs. 18.5±9.9 ㎍/㎗; *p*=0.03) (Table 2).

Table 1. Demographic Characteristics of Patients by Subgroup*

General Characteristics	Relative Adrenal Insufficiency (+)		Relative Adrenal Insufficiency (-)		All Patients	
	Corticosteroid (n=22)	Conservative (n=14)	Corticosteroid (n==20)	Conservative (n=47)	Corticosteroid (n=42)	Conservative (n=61)
Age (yr)	69±15	61±16	70±18	64±14	69±16	64±15
Sex						
Men	16 (73)	6 (43)	16 (80)	34 (72)	32 (76)	40 (66)
Women	6 (27)	8 (57)	4 (20)	13 (38)	10 (24)	21 (34)
Previous disease						
Cardiovascular	10 (45)	6 (43)	7 (35)	18 (38)	17 (40)	24 (39)
Pulmonary	5 (23)	0 (0)	7 (35)	7 (15)	12 (29)	7 (11)
Renal	0 (0)	4 (29)	3 (15)	5 (11)	3 (7)	9 (15)
Liver	0 (0)	0 (0)	2 (10)	2 (4)	2 (5)	2 (3)
Gastrointestinal	0 (0)	0 (0)	1 (5)	0 (0)	1 (2)	0 (0)
Neurological	8 (36)	0 (0)	3 (15)	13 (28)	11 (26)	13 (21)
Endocrinological	7 (32)	7 (50)	8 (40)	17 (36)	15 (36)	24 (39)
None	2 (9)	1 (7)	3 (15)	7 (15)	5 (12)	8 (13)
Admission category						
Unscheduled surgery	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Medical	22 (100)	14 (100)	19 (95)	46 (98)	41 (98)	60 (98)
Scheduled surgery	0 (0)	0 (0)	1 (5)	0 (0)	1 (2)	0 (0)
Acquisition of infection						
Community-acquired	19 (86)	12 (86)	15 (75)	43 (92)	34 (81)	55 (90)
Hospital-acquired	3 (14)	2 (14)	5 (25)	4 (8)	8 (19)	6 (10)
Infection site						
Pulmonary	15 (68)	8 (57)	18 (90)	25 (53)	33 (79)	33 (54)

Genitourinary	1 (5)	3 (21)	4 (20)	5 (11)	5 (12)	8 (13)
Abdominal	5 (23)	7 (50)	3 (15)	16 (34)	8 (19)	23 (38)
Cellulitis	3 (14)	0 (0)	2 (10)	5 (11)	5 (12)	5 (8)
Other	2 (9)	1 (7)	1 (5)	2 (4)	3 (7)	3 (5)
Not documented	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	2 (3)

* Results are based on patient responses to a short corticotropin test. Data are presented as number (percentage) unless otherwise indicated. Plus-minus values are means±standard deviation.

Table 2. Clinical Characteristics of Patients by Subgroup*

Clinical Characteristics	Relative Adrenal Insufficiency (+)			Relative Adrenal Insufficiency (-)			All Patients		
	Corticosteroid (n=22)	Conservative (n=14)	*p*-value	Corticosteroid (n=20)	Conservative (n=47)	*p*-value	Corticosteroid (n=42)	Conservative (n=61)	*p*-value
Temperature (℃)	38.1±0.7	38.2±0.9	0.84	38.0±0.6	38.7±4.8	0.77	38.1±0.7	38.6±4.2	0.44
Heart rate (beats/min)	121±19	113±19	0.38	127±30	124±24	0.90	124±25	122±23	0.69
Mean arterial pressure (mmHg)	98±22	88±16	0.20	100±17	95±18	0.46	99±20	94±18	0.18
Leukocytes (X $10^3/\mu\ell$)	20.9±13.4	16.5±6.4	0.45	17.0±8.1	18.1±10.0	0.78	19.1±11.2	1.8±9.3	0.52
Hemoglobin (mmol/L)	11.2±2.6	11.3±2.4	0.94	10.9±2.2	11.5±2.4	0.36	11.0±2.4	11.4±2.4	0.42
Platelets (X $10^3/\mu\ell$)	222±145	197±141	0.38	231±129	212±148	0.49	226±136	208±145	0.53
Albumin (mg/dℓ)	2.6±0.6	2.7±0.7	0.71	2.7±0.8	2.8±0.4	0.84	2.6±0.7	2.7±0.5	0.33
pH	7.40±0.09	7.44±0.07	0.15	7.41±0.08	7.40±0.09	0.91	7.41±0.09	7.41±0.08	0.99
Bicarbonate (mmol/L)	26.0±9.8	22.6±3.1	0.39	26.4±7.9	23.5±5.9	0.18	26.2±8.9	23.3±5.3	0.04
PaO_2/FiO_2 (mmHg)	173±85	222±87	0.07	208±89	212±105	0.98	190±88	215±101	0.19
ESR (mm/hr)	53±35	54±35	0.83	70±43	54±45	0.26	61±39	54±43	0.41
CRP (mg/dℓ)	14.4±11.7	17.7±10.7	0.28	18.2±12.7	16.8±16.7	0.31	16.2±12.2	17.0±15.4	0.78
APACHE II†	23.4±8.0	26.6±7.6	0.20	21.1±6.9	23.3±6.2	0.15	22.3±7.5	24.1±6.6	0.21
SAPS‡	49.5±13.6	53.1±14.3	0.47	44.5±11.8	51.6±12.7	0.048	47.1±12.9	51.9±12.9	0.06
SOFA§	9.7±4.0	10.4±2.3	0.36	8.3±2.2	10.3±3.8	0.032	9.0±3.4	10.3±3.5	0.07
Number of ventilator care	21 (96)	10 (71)	0.42	20 (100)	42 (89)	0.45	40 (95)	52 (85)	0.25
Time on a vasopressor before corticosteroid (hr)	91.6±111.5	▪	▪	108.2±96.2	▪	▪	99.5±103.6	▪	▪
Incidence of shock onset before ICU admission	19 (86)	10 (71)	0.48	16 (80)	35 (74)	0.64	35 (83)	45 (74)	0.48
Duration from shock onset to ICU admission (days)	2.2±2.8	1.2±1.3	0.67	1.7±2.9	0.9±1.2	0.70	1.9±2.8	0.9±1.2	0.04

Incidence of shock onset after ICU admission	3(14)	4(29)	0.37	4(20)	12(26)	0.55	7(17)	16(26)	0.64
Duration from ICU admission to shock onset (days)	5.0±3.6	11.5±19.7	0.86	3.0±3.4	2.6±2.7	0.95	3.9±3.3	4.8±9.9	0.81
Cortisol concentration (ug/dℓ)									
Before corticotropin stimulation test	24.4±18.8	25.7±13.8	0.53	13.6±5.7	18.5±9.9	0.03	19.3±15.0	20.2±11.2	0.72
30 min after corticotropin stimulation test	27.0±18.2	30.1±10.6	0.13	26.3±9.2	32.6±14.1	0.04	26.7±14.4	31.9±13.4	0.06
60 min after corticotropin stimulation test	28.9±18.9	30±11.6	0.27	27.8±10.4	35.3±16.4	0.08	28.4±15.3	34.0±15.5	0.07
Cortisol increase (ug/dL)	4.9±2.0	6±2.9	0.08	15.5±6.2	18.2±11.0	0.34	9.9±6.9	15.4±11.0	<0.01

* Results are based on patient responses to a short corticotropin test. Data are presented as number (percentage) unless otherwise indicated. Plus-minus values are means±standard deviation
† Acute physiology and chronic health evaluation (APACHE) II ranges from 0 to 67, with higher scores indicating more severe organ dysfunction.
‡ Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.
§ Sequential Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

3. Outcomes

Table 3 shows length (days) of ventilator care, intensive care unit stay, and hospital stay of each group as well as rate of fatal events.

In patients with relative adrenal insufficiency, there were no statistically significant differences in length of ventilator care, intensive care unit stay, and hospital stay between the corticosteroid and conservative groups (22.7±23.4 vs. 26.2±18.0, p=0.35; 23.5±80.9 vs. 22.5±21.2, p=0.86; 38.9±38.5 vs. 33.3±33.4, p=0.71). Likewise, in patients without relative adrenal insufficiency, there were no statistically significant differences in length of ventilator care, intensive care unit stay, and hospital stay between the corticosteroid and conservative groups (28.6±28.1 vs. 23.9±31.1, p=0.49; 28.9±27.0 vs. 26.1±30.2, p=0.42; 49.9±48.1 vs. 39.1±35.2, p=0.29). In all patients, there were also no statistically significant differences in length of ventilator care, intensive care unit stay, and hospital stay between the corticosteroid and conservative groups (25.5±24.7 vs. 24.3±28.9, p=0.84; 26.1±23.9 vs. 25.3±28.3, p=0.88; 44.2±43.2 vs. 37.8±34.6, p=0.41) (Table 3).

For rates of fatal events, there were no significant differences between the 2 treatment groups in rates of death at day 28, intensive care unit stay, and hospital stay among patients with and without relative adrenal insufficiency as well as among all patients (Table 3).

According to Kaplan-Meier analysis of death at day 28 among patients with relative adrenal insufficiency, no significant difference was shown. There were 9 deaths in 22 patients in the corticosteroid group (36.4%; 95% CI, 69.6-

125.9) and 4 deaths in 14 patients in the conservative group (28.6%; 95% CI, 58.6-126.7; p=0.64)(Figure 2A). Among patients without relative adrenal insufficiency, no significant difference was shown. There were 3 deaths in 20 patients in the corticosteroid group (15.0%; 95% CI, 145.1-219.9) and 14 deaths in 47 patients in the conservative group (29.8%; 95% CI, 75.4-109.1; (p= 0.16) (Figure 2B). Overall, there were 11 deaths in 42 patients in the corticosteroid group (26.2%; 95% CI, 131.2-190.0) and 18 deaths in 61 patients in the conservative group (29.5%; 95% CI, 79.1-110.0; p= 0.62), resulting in no statistically significant difference (Figure 2C).

Table 3. Outcomes and Frequency of Fatal Events in Patients by Subgroup*

Outcomes	Relative Adrenal Insufficiency (+)			Relative Adrenal Insufficiency (-)			All Patients		
	Corticosteroid (n=22)	Conservative (n=14)	*p*-value	Corticosteroid (n=20)	Conservative (n=47)	*p*-value	Corticosteroid (n=42)	Conservative (n=61)	*p*-value
Duration (days)									
Ventilator care	22.7±23.4	26.2±18.0	0.35	28.6±28.1	23.9±31.1	0.49	25.5±24.7	24.3±28.9	0.84
Intensive care unit stay	23.5±80.9	22.5±21.2	0.86	28.9±27.0	26.1±30.2	0.42	26.1±23.9	25.3±28.3	0.88
Hospital stay	38.9±38.5	33.3±33.4	0.71	49.9±48.1	39.1±35.2	0.29	44.2±43.2	37.8±34.6	0.41
Fatal Events									
28-day mortality	8 (36)	4 (29)	0.63	3 (15)	14 (30)	0.20	11 (26)	18 (30)	0.71
ICU mortality	11 (50)	6 (43)	0.68	9 (45)	17 (36)	0.50	20 (48)	23 (38)	0.32
Hospital mortality	12 (55)	6 (43)	0.50	9 (45)	19 (40)	0.73	21 (50)	25 (41)	0.37

* Results are based on patient responses to a short corticotropin test. Data are presented as number (percentage) unless otherwise indicated. Plus-minus values are means±standard deviation.

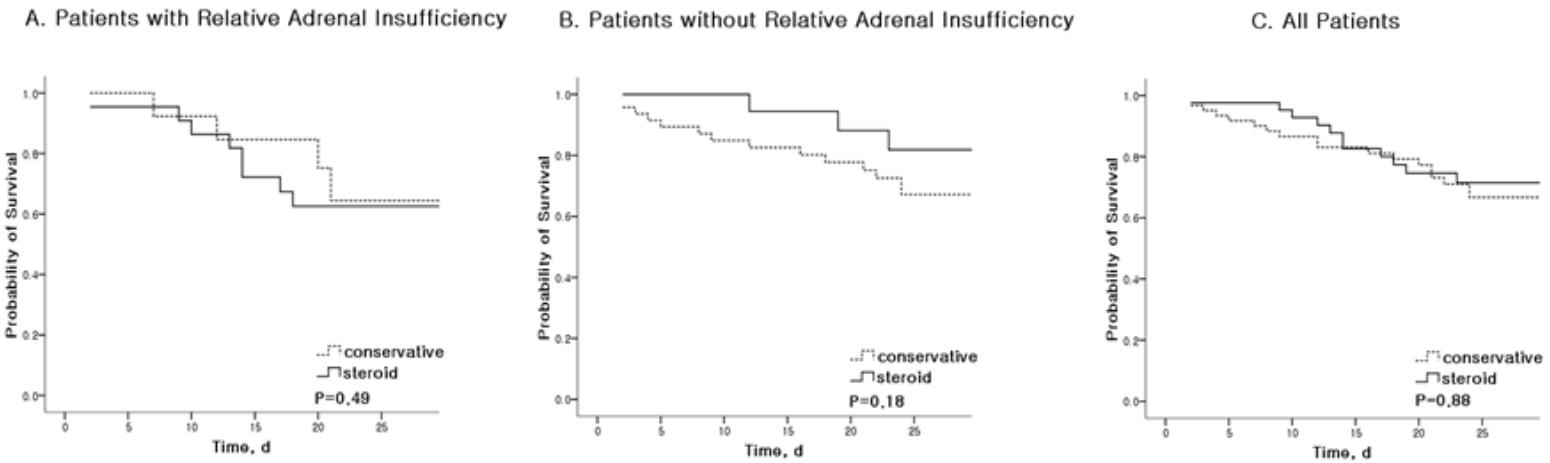

Figure 2. Kaplan-Meier Curves for Survival at Day 28

For the comparison between the corticosteroid and conservative groups, there were no significant differences among patients with relative adrenal insufficiency (Panel A), without relative adrenal insufficiency (Panel B), and all patients who underwent evaluation (Panel C).

4. Comparison between Survivors and Non-survivors at Day 28

There were 74 survivors (71.8%) and 29 non-survivors (28.2%) at day 28. *T*-test was performed to compare the characteristics of survivors and non-survivors. Basal serum cortisol was significantly higher in non-survivors (24.0±13.2 ㎍/㎗ vs. 18.1±12.4 ㎍/㎗; p=0.04). APACHE II, SAPS, and SOFA were also significantly higher in non-survivors than in survivors (26.7±5.7 vs. 22.0±7.1, p<0.01; 55.9±12.7 vs. 47.6±12.6, p<0.01; 12.4±3.8 vs. 8.8±2.8, p<0.01) (Table 4).

Table 4. Comparison between Survivors and Non-survivors at Day 28*

Characteristics	Survivors N=74	Non-survivors N=29	*p*-value
Age (yr)	67±16	63±14	0.27
Basal serum cortisol concentration (ug/dL)	18.1±12.4	24.0±13.2	0.04
Leukocytes (X $10^3/\mu\ell$)	19.2±11.1	16.0±6.3	0.15
Hemoglobin (mmol/L)	11.3±2.4	11.2±2.2	0.79
Platelets (X $10^3/\mu\ell$)	231±133	176±157	0.08
Albumin (g/dL)	2.7±0.5	2.6±0.7	0.23
pH	7.42±0.08	7.38±0.08	0.01
Bicarbonate (mmol/L)	25.2±7.6	22.6±5.3	0.09
PaO_2/FiO_2 (mmHg)	219±104	167±54.8	0.01
ESR (mm/hr)	58.8±42.3	52.7±39.1	0.51
CRP (mg/dL)	17.2±14.7	15.3±12.6	0.53
APACHE II†	22.0±7.1	26.7±5.7	<0.01
SAPS‡	47.6±12.6	55.9±12.7	<0.01
SOFA§	8.8±2.8	12.4±3.8	<0.01

* Plus-minus values are means±standard deviation

† The acute physiology and chronic health evaluation (APACHE) II ranges from 0 to 67, with higher scores indicating more severe organ dysfunction.

‡ Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.

§ Sequential Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

Cox proportional hazards analysis for 28-day mortality showed several statistically significant predictors. Men had a hazard ratio of 2.69 (p=0.04) compared to women, and basal serum cortisol and SOFA score also showed a statistically significant hazard ratio of 1.04 (p<0.01) and 1.23 (p<0.01), respectively (Table 5).

Table 5. Cox Proportional Hazards for 28-day Mortality

	Hazard Ratio	**95% CI***	***p*-value**
Age	1.00	0.98-1.03	0.83
Sex (M)	2.69	1.03-7.08	0.04
Basal serum cortisol concentration (ug/dL)	1.04	1.01-1.06	<0.01
pH	0.05	<0.01-2.04	0.12
APACHE II†	0.99	0.93-1.07	0.94
SAPS‡	0.99	0.95-1.03	0.68
SOFA§	1.23	1.12-1.35	<0.01

* CI, confidence interval.
† Acute physiology and chronic health evaluation (APACHE) II ranges from 0 to 67, with higher scores indicating more severe organ dysfunction.
‡ Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.
§ Sequential Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

5. Comparison between Patients with and without Relative Adrenal Insufficiency

There were 36 patients (34.9%) with relative adrenal insufficiency and 67 (65.1%) without. Basal serum cortisol was significantly higher in patients with relative adrenal insufficiency (24.9±16.8 ㎍/㎗ vs. 17.1±9.1 ㎍/㎗; $p<0.01$) (Table 6). Indicators of disease severity such as APACHE II, SAPS, and SOFA showed no significant differences between the 2 treatment groups ($p=0.18$, 0.61, and 0.64, respectively).

According to multivariate logistic regression analysis for relative adrenal insufficiency, basal serum cortisol was significantly associated with relative adrenal insufficiency with odds ratio of 1.055 for 1 ㎍/㎗ elevation of basal serum cortisol ($p<0.01$) (Table 7).

Table 6. Comparison between Relative Adrenal Insufficiency (+) Group and (-) Group*

Characteristics	Relative Adrenal Insufficiency (+)	Relative Adrenal Insufficiency (-)	*p*-value
	n=36	n=67	
Age (yr)	65.9±15.5	65.9±15.4	0.97
Basal serum cortisol (ug/dL)	24.9±16.8	17.1±9.1	<0.01
Leukocytes (X $10^3/\mu\ell$)	1.9±1.1	1.8±9.4	0.51
Hemoglobin (mmol/L)	11.2±2.5	11.3±2.3	0.89
Platelets (X $10^3/\mu\ell$)	212±142	218±142	0.86
Albumin (g/dℓ)	2.6±0.6	2.7±0.6	0.50
pH	7.42±0.09	7.41±0.08	0.42
Bicarbonate (mmol/L)	24.7±8.0	24.3±6.6	0.81
PaO_2/FiO_2 (mmHg)	192.0±87.6	211.0±100.0	0.34
ESR (mm/hr)	53.6±34.5	58.9±44.7	0.54
CRP (mg/dL)	15.7±11.3	17.2±15.5	0.59
APACHE II†	24.6±7.9	22.6±6.4	0.18
SAPS‡	50.9±13.8	49.5±12.8	0.61
SOFA§	10.0±3.4	9.7±3.5	0.64

* Results are based on patient responses to a short corticotropin test. Plus-minus values are means ± standard deviation.

† Acute physiology and chronic health evaluation (APACHE) II ranges from 0 to 67, with higher scores indicating more severe organ dysfunction.

‡ Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.

§ Sequential Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

Table 7. Multivariate Logistic Regression Analysis for Relative Adrenal Insufficiency

	Odds ratio	**95% CI***	***p*-value**
Age	1.02	0.99-1.04	0.30
Sex (male)	0.97	0.43-2.22	0.94
Basal serum cortisol concentration (ug/dL)	1.06	1.02-1.09	<0.01
pH	14.11	0.15-1359.74	0.26
APACHE II†	1.09	0.99-1.19	0.08
SAPS‡	0.97	0.92-1.01	0.15
SOFA§	1.01	0.87-1.17	0.88

* CI, confidence interval

† Acute physiology and chronic health evaluation (APACHE) II ranges from 0 to 67, with higher scores indicating more severe organ dysfunction.

‡ Simplified Acute Physiology Score (SAPS) II ranges from 0 to 163, with higher scores indicating more severe organ dysfunction.

§ Sequential Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

IV. DISCUSSION

Use of corticosteroid in patients with severe sepsis or septic shock has a long history of controversy. Since the relationship between sepsis and relative adrenal insufficiency was reported, a short corticotropin stimulation test was recommended to identify relative adrenal insufficiency (defined as post-adrenocorticotropic hormone cortisol increase $\leq$9 μg/dℓ) and decide to whom corticosteroid should be administered.[15]

In this study, incidence of relative adrenal insufficiency was 45.6% (36 out of 79 patients who underwent high dose corticotropin stimulation tests), which was lower than a previous Korean report of 70.6% but consistent with recent findings by Sprung et al. (46.7 %).[16, 19]

This study is the first in Korea to evaluate the effects of corticosteroid on survival of patients with and without relative adrenal insufficiency. These results showed that the use of low dose corticosteroid had no significant effects on the rate of death at day 28 in patients with and without relative adrenal insufficiency, which is in contrast to the results by Annane et al. but consistent with those of Sprung et al.[15, 16] The major differences in the reports by Annane et al. and Sprung et al. were the severity of disease in each population, randomization time, and method of corticosteroid treatment. Patients in the study by Annane et al. showed higher SAPS II at baseline (60 in the steroid group, 57 in placebo) and higher rate of death at day 28 in the placebo group (61%).[15] However, the patients in this study showed similar

SAPS II at baseline (47 in the corticosteroid group and 52 in the conservative group vs. 50 in the corticosteroid group and 49 in the conservative group) and similar rate of death at day 28 in the placebo group (30% vs. 32%) to patients in the study by Sprung et al.[16] The time interval between fulfilling entry criteria and corticosteroid administration was much shorter in the Annane et al. study than in this study (4.1 vs. 99.5 hrs) since enrollment time was within 8 hrs after fulfilling entry criteria in the Annane et al.[15] In the study by Sprung et al, they did not state the exact time interval but enrollment was limited to 72 hrs after fulfilling entry criteria, so it should be at least shorter than 99.5 hrs.[16] Therefore, in the study by Annane et al., because administration time corticosteroid to patients was very early, disease status should have been more severe.

As shown above, use of corticosteroid on patients with septic shock is still under debate. Even though several factors causing such different results existed among the studies, immunologic mechanisms and glucocorticoid sensitivity should be taken into consideration.[21] In sepsis or septic shock patients, activity of the hypothalamus-pituitary-adrenal axis and sensitivity to glucocorticoid were regulated. Generally, there was increased sensitivity to glucocorticoid, which might help to protect the organism as a whole through supportive effects on metabolism and vasculature. However, this hypersensitivity was counteracted, possibly at the site of inflammation, by high local concentrations of cytokines such as IL-2 and IL-4 that could decrease glucocorticoid receptor-binding affinity and T-cell response.[21]

Activated corticosteroid receptors also inhibited proinflammatory activity of many growth factors and cytokines by blocking transcription factors required for expression or cellular action of these substances.[4, 22] Consequently, as more severe the inflammation was on going, glucocorticoid might be both beneficial and harmful.

Comparing the method of corticosteroid treatment, it was stopped abruptly after 7 days in the Annane et al. study whereas it was tapered from day 5 to day 11 in the Sprung et al.[15, 16] In this study, corticosteroid was continuously administered for at least 7 days and tapered for a longer period than in the Sprung et al.[16] The reason for tapering instead of abrupt cessation of corticosteroid was to reduce corticosteroid withdrawal symptoms such as hemodynamic and immunologic rebound effects because corticosteroid therapy restores hemodynamic stability and differentially modulates immunologic response to stress in an anti-inflammatory manner rather than immunosuppressive.[23-27] However, longer use of corticosteroid could increase the chance of gastroduodenal bleeding, superinfection, and hyperglycemia.[28] In the study by Sprung et al., more superinfection, including new episodes of sepsis or septic shock, were observed in the corticosteroid group, but there were no significant differences between the 2 treatment groups in the rates of adverse events possibly related to corticosteroid in the study by Annane et al.[15, 16] Moreover, previous reports stated that use of high dose corticosteroid might increase the chance of such complications but there was no significant increase of such complications during low dose corticosteroid treatment.[28-30]

Corticosteroid related adverse events were not observed in this study.

Several authors had shown bad prognosis with increased baseline cortisol, correlating the highest cortisol levels with the most severe illness and the highest risk of mortality.[13, 19, 31, 32] In this study, basal serum cortisol was significantly higher in non-survivors than in survivors and it was also significantly elevated in patients with relative adrenal insufficiency than those without. This result was compatible with the Annane et al. study in which patients with high basal cortisol and no response to corticotropin had the highest risk of death.[13] Moreover, basal serum cortisol was not only a significant predictor of mortality but also of response to corticotropin in this study. Therefore, elevated basal serum cortisol in critically ill patients makes it difficult to diagnose relative adrenal insufficiency.

Time to reversal of shock was not evaluated in this study because vasopressors were tapered at different rates, depending on the attending physicians. Therefore, time could not be an objective measure.

However, there were several limitations in this study. First, the overall number of patients enrolled was small and patients were not evenly distributed into subgroups because of the retrospective study design. Second, because not all patients with relative adrenal insufficiency received corticosteroid and some patients without relative adrenal insufficiency did, smaller number of patients were regrouped into subgroups. Third, the time that the corticotropin stimulation test was done and the time interval between the corticotropin stimulation test and corticosteroid given varied. The duration

of corticosteroid treatment and tapering methods were also different in each patient. All of these factors showed inconsistent corticosteroid treatments in patients with septic shock. Even though attending physicians tried to manage patients according to the sepsis management guideline, the possibility of different management styles could not be ignored. Lastly, enrolled patients had been admitted to hospitals mainly due to medical problems so these results might not be applicable to surgical patients.

In summary, use of corticosteroid did not show beneficial effects on survival of patients with septic shock, either overall or in patients who did not have relative adrenal insufficiency.

V. CONCLUSION

Corticosteroid did not improve survival of patients with septic shock regardless of relative adrenal insufficiency. Therefore, neither replacement of corticosteroid nor corticotropin stimulation test could be applied to all patients with septic shock whether it was accompanied by relative adrenal insufficiency. Considering previous reports and differences in severity of diseases in the population, very early corticosteroid administration could be recommended to patients with very high level of disease severity, but further studies are needed on this issue. In addition, basal serum cortisol was not only a significant predictor of mortality but also of response to short corticotropin stimulation test.

REFERENCES

1. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. Crit Care Med 1995;23:1294-303.

2. The Veterans Administration Systemic Sepsis Cooperative Study Group. 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 1987;317:659-65.

3. Hahn EO, Houser HB, Rammelkamp CH Jr., Denny FW, Wannamaker LW. Effect of cortisone on acute streptococcal infections and poststreptococcal complications. J Clin Invest 1951;30:274-81.

4. Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med 1993;119:1198-208.

5. Nakano T, Ohara O, Teraoka H, Arita H. Glucocorticoids suppress group II phospholipase A2 production by blocking mRNA synthesis and post-transcriptional expression. J Biol Chem 1990;265:12745-8.

6. O'Banion MK, Winn VD, Young DA. cDNA cloning and functional activity of a glucocorticoid-regulated inflammatory cyclooxygenase. Proc Natl Acad Sci U S A 1992;89:4888-92.

7. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993;329:2002-12.

8. Weitzman S, Berger S. Clinical trial design in studies of corticosteroids for bacterial infections. Ann Intern Med 1974;81:36-42.

9. Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 1976;184:333-41.

10. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653-8.

11. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. N Engl J Med 1984;311:1137-43.

12. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991;337:582-3.

13. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283:1038-45.

14. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997;337:1285-92.

15. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B,

Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.

16. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.

17. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17-60.

18. Lee KS, Baik SH, Lee HN, Park JH, Oh YJ, Sheen SS, et al. Significance of Corticosteroids and Their Relationship with Other Parameters in Patients with Sepsis. Tuberc Respir Dis 2006;61:356-65.

19. Kwon YS, Suh GY, Kang EH, Koh WJ, Chung MP, Kim H, et al. Basal Serum Cortisol Levels are not Predictive of Response to Corticotropin but Have Prognostic Significance in Patients with Septic Shock. J Korean Med Sci 2007;22:470-5.

20. Fauci AS. Harrison's principles of internal medicine 17th ed. New York: McGraw-Hill Medical; 2008. P.1696.

21. Molijn GJ, Spek JJ, van Uffelen JC, de Jong FH, Brinkmann AO, Bruining HA, et al. Differential adaptation of glucocorticoid sensitivity of peripheral blood mononuclear leukocytes in patients with sepsis or septic shock. J Clin Endocrinol Metab 1995;80:1799-803.

22. Chrousos GP, Detera-Wadleigh SD, Karl M. Syndromes of glucocorticoid resistance. Ann Intern Med 1993;119:1113-24.

23. Keh D, Weber-Carstens S, Bonke T, Schulz C, Pettersson M, Ahlers O, et al. Effects of hydrocortisone stress-dose therapy in septic shock (part I): influence on hemodynamic stability and plasma nitrite/nitrate levels. Critical Care 1999;3 Suppl 1:104.

24. Bercker S, Ahlers O, Keh D, Pettersson M, Schulz C, B?nke T, et al. Effects of stress-dose hydrocortisone therapy in septic shock (part II): soluble E-selectin and interleukin-6. Preliminary results of a double blinded, randomized, placebo-controlled cross-over study. Critical Care 1999;3 Suppl 1:105.

25. Bonke T, Schulz C, Keh D, Pettersson M, Weber-Carstens S, Ahlers O, et al. Effects of stress-dose hydrocortisone therapy in septic shock (part III): monocyte HLA-DR expression and blood interferon-γ concentration. Preliminary results of a double blinded, randomized, placebo-controlled cross-over study. Critical Care 1999;3 Suppl 1:106.

26. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167:512-20.

27. Briegel J, Kellermann W, Forst H, Haller M, Bittl M, Hoffmann GE, et al. Low-dose hydrocortisone infusion attenuates the systemic

inflammatory response syndrome. The Phospholipase A2 Study Group. Clin Investig 1994;72:782-7.

28. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ 2004;329:480.

29. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med 2004;141:47-56.

30. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671-84.

31. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995;23:78-83.

32. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003;31:141-5.

ABSTRACT (IN KOREAN)

중환자실 내 패혈성 쇼크 환자에서 부신 기능 저하의 발생 및 예후

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배경:

패혈증과 상대적 부신 기능 부전의 관계가 알려지면서, 상대적 부신 기능 부전을 진단하고 코르티코스테로이드 투여가 필요한 환자를 선별하기 위해서, short corticotropin stimulation test 를 시행하고 있다. 이번 연구의 목표는 패혈성 쇼크가 있는 환자 중 상대적 부신 기능 부전이 있는 군과 없는 군 내에서 코르티코스테로이드 사용에 따른 효과를 평가하고자 하였다.

대상 및 방법:

2005 년 6 월부터 2007 년 12 월까지, 세브란스 병원의 중환자실로 입원한 환자 중 지속적인 패혈성 쇼크로 short

corticotropin stimulation test 를 시행한 103 명의 환자를 대상으로 후향적 연구를 진행하였다.

결과:

103명 중, 36명(34.9%; 코르티코스테로이드 치료군:22명; 보존적 치료군:14명)은 상대적 부신 기능 부전을 보였으며, 67명(65.1%; 코르티코스테로이드 치료군:20명; 보존적 치료군:47명)은 상대적 부신 기능 부전을 보이지 않았다. 상대적 부신 기능 부전이 있는 군(36% vs. 29%; p=0.63)과 없는 군(15% vs. 30%; p=0.20) 모두에서 코르티코스테로이드 치료군과 보존적 치료군 사이에 28일 사망률의 차이는 보이지 않았다. 기저 혈청 코르티졸은 생존자에 비해 비생존자에서 (24.0 ± 13.2 ㎍/dℓ vs 18.1 ± 12.4 ㎍/dℓ; p=0.04) 그리고 상대적 부신 기능 부전이 없는 군보다 있는 군(24.9 ± 16.8 ㎍/dℓ vs 17.1 ± 9.1 ㎍/dℓ; p<0.01)에서 통계학적으로 의미 있게 높았다.

결론:

코르티코스테로이드는 상대적 부신 기능 부전과 상관없이 패혈성 쇼크 환자에서 생존율을 향상시키지 못했다. 따라서, 코르티코스테로이드 투여 대상 환자 선별을 위한 short corticotropin test 시행은 도움이 되지 않을 것이다. 또한,

기저 혈청 코르티솔은 환자 사망 및 short corticotropin test 에 대한 반응을 예측할 수 있는 통계학적으로 의미 있는 예측 인자였다.

핵심되는 말 : 부신 기능 부전, 코르티코스테로이드, 패혈성 쇼크