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Effect of stress doses of hydrocortisone on S-100B vs. interleukin-8 and polymorphonuclear elastase levels in human septic shock

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Abstract

Stress doses of hydrocortisone are known to have immunomodulatory effects in patients with hyperdynamic septic shock. The prognosis correlates with the presence and severity of septic encephalopathy. However, neurological evaluation is influenced by the use of analgesia sedation during artificial ventilation. The objective of this study was to demonstrate the effect of stress doses of hydrocortisone during the initial phase of human septic shock on the serum values of the neurospecific protein S-100B in comparison to the inflammation markers interleukin (IL)-8 in serum and polymorphonuclear (PMN) elastase in plasma. A total of 24 consecutive patients, who met the American College of Chest Physicians/Society of Critical Care Medicine criteria for septic shock, were enrolled in this prospective, randomized, double-blind, single-center trial. The severity of illness at recruitment was graded using the Acute Physiology and Chronic Health Evaluation II and the Simplified Acute Physiology Score II scoring systems. Multi-organ dysfunction syndrome was described by the Sepsis-related Organ Failure Assessment (SOFA) score. All patients were prospectively randomized to receive either stress doses of hydrocortisone or placebo. Hydrocortisone was started in 12 patients with a loading dose of 100 mg and followed by a continuous infusion of 0.18 mg/kg/h for 6 days. Median S-100B serum levels of the hydrocortisone group decreased from 0.32 ng/mL at study entry to 0.07 ng/mL 6 days later without significant differences compared to the placebo group. Initial IL-8 serum levels were significantly higher in the hydrocortisone group up to 12 h after study entry, and significantly decreased from 715 to 17 pg/mL at the end of the observation period. Median PMN elastase plasma levels were not affected by hydrocortisone infusion. Patients with initial S-100B serum levels >0.50 ng/mL revealed significantly higher SOFA scores up to 30 h, IL-8 serum levels up to 12 h, and PMN elastase plasma levels up to 36 h after study entry than those patients with ≤ 0.50 ng/mL. These effects were independent of the amount of fluid correction for hemodilution. Starting S-100B, IL-8 and PMN elastase values of the hydrocortisone group were within the ranges already known in patients with out-of-hospital cardiac arrest or severe traumatic brain injury. Stress doses of hydrocortisone resulted in a significant reduction in IL-8 serum, but not in S-100B serum and PMN elastase plasma concentrations in patients with hyperdynamic septic shock. For the first time, a similar extent of S-100B increase in serum of septic patients at the time of diagnosis was shown as reported for cardiac arrest or severe traumatic brain injury.

Keywords: cerebral ischemia; hydrocortisone; inflammation; septic shock; S-100B.

Introduction

The endogenous glucocorticoid hydrocortisone plays a pivotal role in modulation of the immune response to sepsis (1). Low-dose hydrocortisone infusions may attenuate this systemic inflammatory response, as judged by clinical signs and inflammatory markers (2–4). Two double-blind, single-center trials demonstrated that stress doses of hydrocortisone reversed septic shock, as defined by cessation of vasopressor therapy. The earlier weaning from vasopressor therapy in septic shock was associated with improvements in organ dysfunction and mortality rates (5, 6).

Apart from failure of many vital parenchymal organs, critical illness myopathy or dysfunction of peripheral nerves, septic shock may cause serious brain damage and septic encephalopathy (7–10). Septic encephalopathy represents a multifocal or diffuse cerebral malfunction, which may occur in the context of a systemic infection without direct traumatic affection of the brain (11–14). The prognosis for septic patients clearly correlates with the presence and severity of encephalopathy. Mortality in patients without encephalopathy varies between 0% and 26% (11) and amounts to nearly 50% in patients with severe symptoms of encephalopathy. Although the severity of the systemic infection seems to be responsible for the high mortality rate rather than the encephalopathy itself, an increase in mortality rate was reported in relation to the Glasgow-Coma-Scale (GCS) score in 50 patients with septic encephalopathy (14). This

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score is still used for the evaluation of neurological dysfunction and prognosis throughout the course of multi-organ failure (MOF) (15, 16). However, since determination of the GCS score in septic shock is clearly influenced by the use of analgesia sedation during artificial ventilation, the evaluation of a reliable biochemical marker, which could supply evidence for encephalopathy in the initial phase of sepsis and before the occurrence of clinically leading symptoms, seems meaningful.

Measurement of the neuroprotein S-100B released into the circulation was considered as a reliable procedure in detecting brain damage due to isolated traumatic brain injury (17), stroke (18), hemorrhage (19) or global ischemia (20, 21). Increased S-100B serum levels have also been observed to correlate with the duration of cardiopulmonary bypass surgery (22) and the associated development of neurological complications (23, 24). S-100B is physiologically localized in the cytosol or bound to the membranes of astroglial cells, mostly of the central nervous system (25). If these cells are damaged, S-100B is rapidly released, leaking into the cerebrospinal fluid and secondarily across the blood-brain barrier into the circulation. The protein is eliminated by the kidney with a biological half-life between 30 and 113 min (26, 27). Continuously increasing S-100B serum levels after brain injury may reflect both early cellular damage due to impaired permeability of the blood-brain barrier (24) and delayed renal elimination.

The objective of our study, which was part of a double-blind trial, was to analyze the effect of stress doses of hydrocortisone on circulating S-100B as a possible measure of neurological dysfunction in patients during the initial phase of hyperdynamic septic shock, and to compare these results with the profile of two well-known inflammation parameters [interleukin-8 (IL-8) and polymorphonuclear (PMN) elastase] in the circulation.

Materials and methods

Study design and subjects

The study protocol was approved by the institutional Review Board of the Ludwig-Maximilians-University of Munich. Relatives of the patients were informed regarding the medical problems, as well as the nature and purpose of the study, and served as surrogates to determine the judgment of unconscious patients with respect to participation in the study. The study was conducted in the multidisciplinary intensive care unit (ICU) of the Department of Anesthesiology Munich-Grosshadern in the university hospital.

Patients suffering from septic shock were prospectively enrolled if they were on vasopressor support and met the criteria for septic shock proposed by the members of the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference Committee (28): documented infection or positive blood culture; at least two symptoms of the systemic inflammatory response syndrome, such as fever (body temperature $>38°C$) or hypothermia (body temperature $<36°C$), tachycardia (>90 beats/min), tachypnea (>20 breaths/min) or hyperventilation [$PaCO_2$ <32 torr (4.33 kPa)], and abnormal white blood cell counts [$>12{,}000$ cells/mm^3 or $<4{,}000$ cells/mm^3 or immature neutrophils (bands $>10\%$)] evidence of organ dysfunction or hypoperfusion abnormality; and persistent sepsis-induced hypotension despite adequate fluid resuscitation or the use of inotropic or vasopressor support.

Fluid resuscitation was considered to be adequate when the pulmonary capillary wedge pressure (PCWP) reached values between 12 and 15 mm Hg. Referring to the SCCM guidelines, only patients on vasopressor support and with high-output circulatory failure defined by a cardiac index (CI) >4.0 L/min/m^2 (in patients >55 years, >3.5 L/min/m^2 due to reduced cardiac output with age) were randomized to the treatment groups. The hypercirculatory state had to be present without the use of positive inotropic agents such as dobutamine, dopexamine or epinephrine. Patients who were treated with vasopressors for >72 h or with glucocorticoids were not included. The definition of the target population was based on data from a pilot study (29); the study design and patient treatment routine have already been described (5).

Vasopressor therapy was titrated to achieve a mean arterial pressure (MAP) of >70 mm Hg. If dopamine exceeded a dose of 10 μg/kg/min, norepinephrine combined with dopamine in low dose (2–4 μg/kg/min) was the proposed drug option. After randomization, however, the attending physicians were free to use additional catecholamines such as epinephrine, dobutamine, or dopexamine. When septic shock reversed, norepinephrine or epinephrine was tapered off in steps of 0.02–0.03 μg/kg/min (5).

Infections were diagnosed according to clinical and microbiological criteria. Suspected infection at the time of enrolment was proven by clinical or microbiological examination. Bacterial infections were treated with selective antibiotic regimens, with preference given to third-generation cephalosporins, the carbapenem imipenem-cilastin, or the quinolone ciprofloxacin. Bacterial and fungal cultures (respiratory secretions, urine, peritoneal fluid, and wound swabs) were routinely assayed on fixed days twice each week. In addition, swabs of the peritoneum were taken from each quadrant of the abdomen in cases of surgery. In cases of new or unexplained fever ($>38.5°C$), two blood cultures were taken by intravenous puncture, and all venous and arterial catheters were changed. The tips of all catheters were examined for colonies of bacteria or fungi. Bronchoscopy with bronchoalveolar lavage and protected-brush specimens was carried out in cases of new pulmonary infiltrates indicated on the chest radiograph. Selective decontamination of the nasooropharynx and the digestive tract was performed throughout the period spent in the ICU using a regimen of polymyxin B (50 mg every 6 h) and gentamicin (80 mg every 6 h) dissolved in 10 mL of 0.9% saline. A 1-mL aliquot of this solution was instilled into each nostril, 3 mL into the oropharynx, and 5 mL via a nasogastric tube into the stomach (5).

The severity of illness at the time of enrolment was determined using the Acute Physiology and Chronic Health Evaluation (APACHE) II and III, and Simplified Acute Physiology scoring (SAPS) systems. The primary study endpoint was the time to shock reversal, as defined by cessation of vasopressor support. Secondary endpoints were hyperdynamic alteration, multiple-organ dysfunction syndrome, systemic inflammatory response, and evolution of coagulation disorders (5).

During controlled ventilation and treatment with antibiotics, infusions, and systemic vasopressor support in the ICU, anesthesia aimed at a constant GCS score of 3 points was achieved by titration of midazolam and fentanyl. Therefore, the neurological investigation had to be limited to the exam-

ination of reflexes. When the sedative drugs were reduced, the actual GCS score was recorded, using the grading proposed for patients on mechanical ventilation (30). The Sepsis-related Organ Failure Assessment (SOFA) score, which was published in 1996 (31), was added to the study protocol by amendment and retrospectively calculated from the raw data.

Interventions

A total of 24 patients were prospectively randomized to receive infusions of either stress doses of hydrocortisone (n = 12) or placebo (n = 12). Hydrocortisone administration was started with a loading dose of 100 mg, administered intravenously in 30 min, followed by continuous infusion of 0.18 mg/kg/h. According to the SCCM guidelines, either continuous infusion of 200–300 mg hydrocortisone/day for 7 days with subsequent dose reduction, or low-dose application of 50–75 mg hydrocortisone four times a day is recommended for the management of patients with septic shock (32). After reversal of septic shock (defined as dopamine doses of <6 μg/kg/min or cessation of norepinephrine/epinephrine infusion) the dose of hydrocortisone was reduced to 0.08 mg/kg/h. This dose was kept constant for 6 days. As soon as the underlying infection had been treated successfully or the sodium serum concentrations had increased to >155 mmol/L, the hydrocortisone infusion was tapered off in steps of 24 mg/day. Physiological saline solution was used as placebo. To conduct the study in a double-blind manner, the study drugs were prepared by research assistants at our institution, who were not involved in the study or in the clinical care of the patients. Study drug preparation has been already described (5).

For continuous venovenous hemofiltration (CVVH; n = 10) blood was taken from the subclavian, internal jugular, or femoral vein, and a blood pump was used to perfuse the filtration membrane. The dialysate compartment of the membrane unit was under negative pressure relative to the blood compartment, which permitted hydraulic ultrafiltration of excess fluid across the membrane. Dialyzed blood was returned to the patient through tubing with an air embolus protector. To prevent clotting in the extracorporeal circuit, heparin was given to produce full systemic anticoagulation (whole blood clotting time >30 min). Anticoagulation was permanently monitored, and the heparin dose was subsequently individualized.

Blood sampling and biochemical measurements

The first blood samples were taken at study entry in the ICU [point of measurement (PM)1]. Subsequently, blood samples were drawn every 6 h (PM2–9) during the next 2 days, and once a day throughout the following 4 days (PM10–13). All specimens were converted to serum or citrated plasma, centrifuged with 3000 U/min for 10 min at room temperature, and frozen in aliquots at -70°C until batch evaluation.

S-100B serum levels were analyzed by means of an immunoluminometric assay (LIAMAT® Sangtec®100; Byk-Sangtec Diagnostica, Dietzenbach, Germany) with a lower detection limit of 0.02 ng/mL and a cut-off level of <0.12 ng/mL for normal values. IL-8 serum values were determined using a quantitative ELISA (IL-8 Milenia; Milenia Biotec, Bad Nauheim, Germany) with a detection limit of 0.5 pg/mL and a normal range of 0–30 pg/mL. Plasma levels of PMN elastase complexed with α_1-proteinase inhibitor were quantified by means of a specific two-site ELISA (PMN Elastase Milenia; Milenia Biotec; normal values 19–78 ng/mL).

Total serum protein concentrations were measured with a specific microprotein assay kit (Micro BCA Protein Assay; Pierce, Rockford, IL, USA) in order to avoid interferences with possible hemodilution. Due to logistic reasons (limited sample size) we had to use the BCA assay instead of the Biuret total protein assay. In addition, the C-reactive protein (CRP) serum levels (mg/dL), as well as the creatinine serum levels (mg/dL) and fluid balance (mL) per 24 h were calculated to identify the amount of fluid correction for hemodilution.

Statistical analysis

All demographic and biochemical data are presented as median and interquartile range (IQR; 25th–75th percentile). Group differences at each point of measurement were accomplished by means of a Mann-Whitney U-test or Wilcoxon test due to non-normal distribution of the data. The Kaplan-Meier method was used to determine the probability of being on vasopressor therapy over time. The failure times until cessation of vasopressor therapy were compared using a generalized Wilcoxon (Breslow) test.

The entire study group was differentiated into subgroups 1 (>0.50 ng/mL) and 2 (≤ 0.50 ng/mL) with respect to S-100B levels at study entry. Biochemical data for septic patients were compared to those reported for patients with out-of-hospital cardiac arrest or isolated severe traumatic brain injury (GCS score ≤ 8 points), and healthy volunteers without a history of brain or cardiac damage (17, 21, 33). Blood sampling of the control groups was carried out after informed consent. The statistical analysis was performed using SPSS version 12.0 (SPSS GmbH Software, Munich, Germany), and a two-tailed p-value of <0.05 was considered to be significant.

Results

Demographic and clinical characteristics of the study groups

A total of 12 patients were assigned each to the therapy group receiving stress doses of hydrocortisone (H) and to the placebo (P) group, respectively (5). The characteristics of both patient groups did not differ according to demographic data, severity of the illness and the degree of organ dysfunction (Table 1). In addition, no significant differences occurred concerning CVVH application, length of artificial ventilation and survival rate after 28 days between the groups.

Shock reversal was achieved in 11 of the 12 patients treated with hydrocortisone vs. 9 of the 12 patients treated with placebo. The median time of vasopressor support in group H [2 days (IQR 1–6)] was significantly reduced compared to group P [7 days (3–19); Figure 1]. Specific analysis revealed significant increases in terms of mean arterial pressure and systemic vascular resistance, and showed a trend to earlier resolution of the organ dysfunction syndrome in group H (5).

No differences were evident between the groups regarding the type and anatomical site of the underlying infection. The primary cause of septic shock was peritonitis in 9 patients (4 in group H, 5 in group P)

Table 1 Characteristics of septic shock patients randomized into hydrocortisone (n = 12) and placebo (n = 12) groups.

Characteristic	Group		p
	Hydrocortisone (n = 12)	Placebo (n = 12)	
Age, years	41 (30–65)	54 (47–57)	0.410
Male, %	58	50	0.755
APACHE II score, points	25 (20–28)	28 (18–32)	0.590
APACHE III score, points	85 (71–104)	85 (53–112)	0.671
SAPS II score, points	53 (46–60)	48 (42–76)	0.630
CVVH, %	42	42	1.000
Length of ventilation, days	16 (12–24)	21 (8–38)	0.755
Mortality rate, %	25	42	0.514
Primary cause of sepsis			
Peritonitis, %	33	42	0.466
Pneumonia, %	58	50	0.755
Baseline values			
S-100B, ng/mL	0.32 (0.19–3.60)	0.41 (0.18–0.70)	0.062
IL-8, pg/mL	715 (156–6275)	94 (68–948)	<0.010*
PMN elastase, ng/mL	637 (496–1680)	522 (173–674)	0.058
CRP, mg/dL	25 (22–33)	19 (13–36)	0.148
Creatinine, mg/dL	1.2 (0.8–2.3)	1.0 (0.7–1.8)	0.563
Fluid balance, mL	2200 (25–4188)	2500 (580–4025	0.870

Age, scores and days of ventilation are presented as median and interquartile range (25%–75% percentile). *Significant difference between groups in the Mann-Whitney U-test.

and pneumonia in 13 patients (7 in group H, 6 in group P). In all nine subjects, peritonitis required at least one surgical intervention, which was applied in a timely manner, in most cases immediately after study entry. One patient each suffered from meningitis and severe soft tissue infection, respectively. The initial antibiotic treatment was inadequate in seven patients (3 in group H, 4 in group P) and was corrected according to the results of the microbiological examinations.

S-100B/IL-8 serum and PMN elastase plasma levels after randomization in hydrocortisone or placebo group

Baseline median S-100B, IL-8, and PMN elastase levels were considerably elevated for both groups compared to values for healthy individuals (Figure 2). After hydrocortisone infusion, only median serum concentrations of IL-8 decreased significantly from 715 pg/mL (156–6275 pg/mL) to 17 pg/mL (12–32 pg/mL) at the end of the observation period, reaching the normal range by 18 h after study entry [28 pg/mL (16–121 pg/mL); PM4]. In contrast, S-100B serum and PMN elastase plasma levels in group H were not significantly affected over time (Figure 2). Similarly, serum concentrations of S-100B and IL-8, as well as plasma concentrations of PMN elastase in group P did not significantly decrease during the observation period.

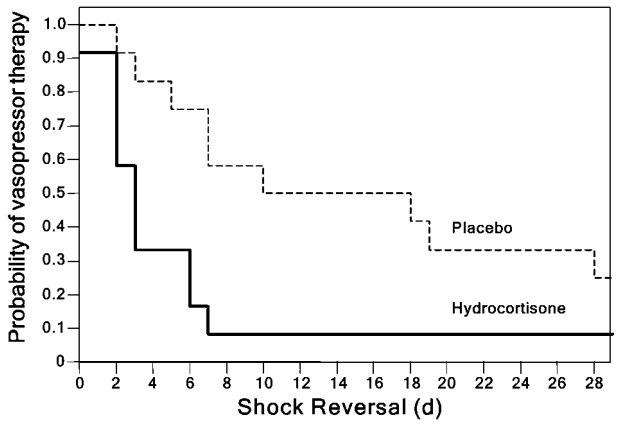

Figure 1 Kaplan-Meier curves showing the probability of being on vasopressor therapy during the course of the study. Comparisons between the time distribution of both treatment groups were performed by means of generalized Wilcoxon (Breslow) test; p = 0.006.

Median S-100B serum levels in group H decreased from 0.32 ng/mL (0.19–3.60 ng/mL) at study entry to 0.07 ng/mL (0.04–0.32 ng/mL) 6 days later, without significant differences compared to group P. Only S-100B levels at PM3 (12 h after study entry) at 0.87 ng/mL (0.14–2.63 ng/mL) were significantly higher in group H compared to 0.37 ng/mL (0.14–0.77 ng/mL) in group P (Figure 2). Initial median IL-8 serum levels in group H were significantly higher compared to group P only from study entry [715 pg/mL (156–6275 pg/mL)] until 12 h later [49 pg/mL (33–428 pg/mL)]. Median PMN elastase plasma levels did not differ between the groups with time, although PMN elastase values from PM1 (study entry) to PM4 (18 h after study entry) were slightly higher in group H than in group P (Figure 2).

Median CRP serum values in both groups were significantly elevated compared to those in healthy individuals. Only median CRP levels in group H significantly decreased from 25 (22–33) to 14 (8–20) mg/dL 3 days after study entry (PM10) and to 7 (2–13) mg/dL at the end of the observation period, but did not reach the normal range (Figure 2). Although CRP values in group H were slightly higher from PM1 (study entry) to PM8 (42 h after study entry), median

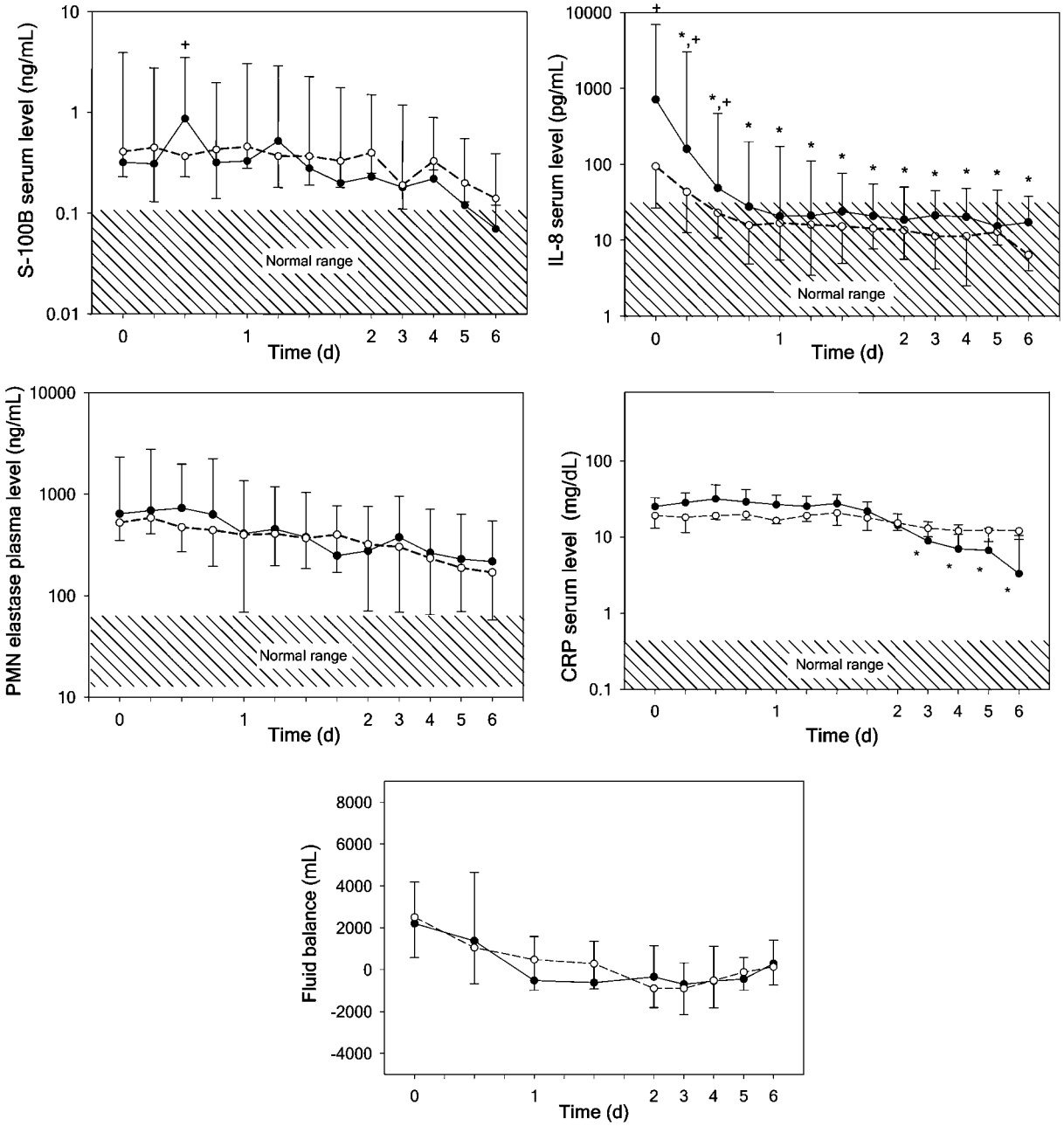

Figure 2 Serum S-100B, IL-8, and plasma PMN elastase levels, as well as serum CRP levels and fluid balance within the first 6 days of septic shock. Patients were randomized in the hydrocortisone group (n = 12; •; data are given as line and scatter plots presenting median and 75th percentile) or the placebo group (n = 12; ○; data are given as line and scatter plots presenting median and 25th percentile). The upper normal value amounts to 0.12 ng/mL for S-100B, to 30 pg/mL for IL-8, to 78 ng/mL for PMN elastase and to 0.5 mg/dL for CRP. The first blood samples were taken at study entry at the ICU. Subsequent blood samples were drawn every 6 h during the next 2 days, and once a day throughout the following 4 days. $+p < 0.05$ represents significant group differences between the two randomized groups. $*p < 0.05$ shows significant differences compared to the baseline levels at study entry.

serum CRP and fluid balance (Figure 2), as well as baseline creatinine levels, did not differ between the groups (Table 1).

SOFA score, IL-8 serum and PMN elastase plasma levels depending on the initial S-100B serum levels

As shown in Table 2, patients in subgroup 1 (n = 8; initial S-100B serum level > 0.50 ng/mL) showed no statistical differences concerning age, gender, SAPS II score, or administration of hydrocortisone when compared to those in subgroup 2 (n = 16; initial S-100B serum level ≤ 0.50 ng/mL). In contrast, the APACHE II and APACHE III score, CVVH application, days required for artificial ventilation, and mortality rate after 28 days were significantly higher in subgroup 1 patients (Table 2).

The median S-100B serum levels in subgroup 1 were always significantly higher than in subgroup 2 (Figure 3). Interestingly, the initial, highly elevated S-100B values in subgroup 1 of 2.60 ng/mL (1.52–5.89 ng/mL) were within the data ranges recently demonstrated for patients with out-of-hospital car-

Table 2 Characteristics of septic shock patients with pathologically elevated initial S-100B serum levels >0.50 ng/mL (subgroup 1) and ≤0.50 ng/mL (subgroup 2).

Characteristic	Subgroup		p
	1 (n=8)	2 (n=16)	
Age, years	41 (30–52)	55 (33–66)	0.070
Male, %	50	50	1.000
APACHE II score, points	28 (25–29)	22 (18–27)	0.016*
APACHE III score, points	98 (74–141)	75 (54–87)	0.029*
SAPS II score, points	65 (46–89)	48 (42–54)	0.070
CVVH, %	75	19	0.020*
Length of ventilation, days	24 (14–32)	14 (6–20)	0.038*
Hydrocortisone, %	63	44	0.482
Mortality rate, %	50	25	0.046*

Age, scores and days of ventilation are presented as median and interquartile range (25th–75th percentile). *Significant difference between groups in the Mann-Whitney U-test.

diac arrest or severe traumatic brain injury (21, 33). Furthermore, median S-100B serum levels in subgroup 2 decreased to 0.05 ng/mL (0.02–0.18 ng/mL) at PM13, and were still elevated compared to the value for healthy controls of 0.04 ng/mL (0.01–0.08 ng/mL) (17).

Patients in subgroup 1 showed higher median SOFA scores than those in subgroup 2 during the observation period, but the differences were significant only from PM1 to PM6 (Figure 3).

Subgroup 1 showed only significantly higher median IL-8 serum levels from PM1 to PM3 compared to subgroup 2. From PM4 to the end of the observation period, median IL-8 serum levels were similar in both subgroups, and ranged within standard values by 24 h after study entry (PM5). Highly increased PMN elastase values declined in both subgroups with time, but remained clearly elevated above the normal range at the end of the observation period. However, patients in subgroup 1 showed significant differences in PMN elastase plasma levels compared to subgroup 2 only from study entry (PM1) to 36 h later (PM7).

Median CRP serum values remained clearly elevated in both subgroups during the entire observation period. Only CRP levels in subgroup 2 significantly decreased from 25 mg/dL (18–41 mg/dL; PM1) to 14 mg/dL (9–21 mg/dL) 3 days after study entry (PM10) and to 9 mg/dL (5–13 mg/dL) 5 days after study entry (PM12). However, median serum CRP and fluid balance did not differ between the subgroups (Figure 3).

Discussion

Clinical sequelae of hyperdynamic septic shock are organ dysfunction, such as mental disorders, disseminated intravascular coagulation, acute lung injury, renal failure, acute hepatic dysfunction, and cardiovascular dysfunction (31). The physiological function of hypercortisolemia associated with stress is to modulate the normal defense mechanisms, thus protecting the host from overactivation of inflammatory reactions (34). Cortisol interacts with the immune system at several levels, exerting suppressive and permissive effects. In a dose-dependent manner, corticosteroids inhibit proinflammatory cytokine synthesis and cellular immunity (35).

Since we observed mineralocorticoid effects of hydrocortisone infusion by measuring serum sodium and potassium concentrations, mineralocorticoids were not added to the treatment (5). Stress levels of cortisol increase sodium retention and produce hypertension in healthy humans. This effect is mediated by Type I and Type IV corticoid receptors (36). The increase in sodium concentrations in the hydrocortisone-treated group in this study suggests that mineralocorticoid effects of hydrocortisone contribute to improved vasopressor response (5).

One major finding of this study is that hydrocortisone administered in stress doses selectively reduced circulating IL-8 serum levels, but not S-100B serum and PMN elastase plasma levels in patients with hyperdynamic septic shock. This effect is obviously independent of the extent of fluid correction for hemodilution. Cytokines are peptides that primarily regulate the interaction and communication of cells of the immune system. In cases of infection, cytokines initiate the systemic inflammatory response by interacting with specific receptors on inflammatory target cells (1). IL-8, which is predominantly discharged from activated macrophages and endothelial cells into the circulation, represents an important chemoattractant for neutrophil granulocytes. During the whole-body inflammation in septic shock, these granulocytes release destructive superoxide anions and lysosomal enzymes such as PMN elastase upon activation (37–40). Since significant differences between patients receiving hydrocortisone or placebo were shown only for IL-8 serum concentrations compared to baseline levels, hydrocortisone does not seem to have a substantial influence on the release of PMN elastase in hyperdynamic septic shock.

However, the clinical data from this therapy study agree very well with results from other reports (2, 6). A significant improvement in the hemodynamic situation, i.e., an increase in mean arterial pressure and systemic vascular resistance, associated with a clear reduction of the need for catecholamines could be observed after application of stress doses of hydrocortisone instead of placebo (Figure 1). The reversal

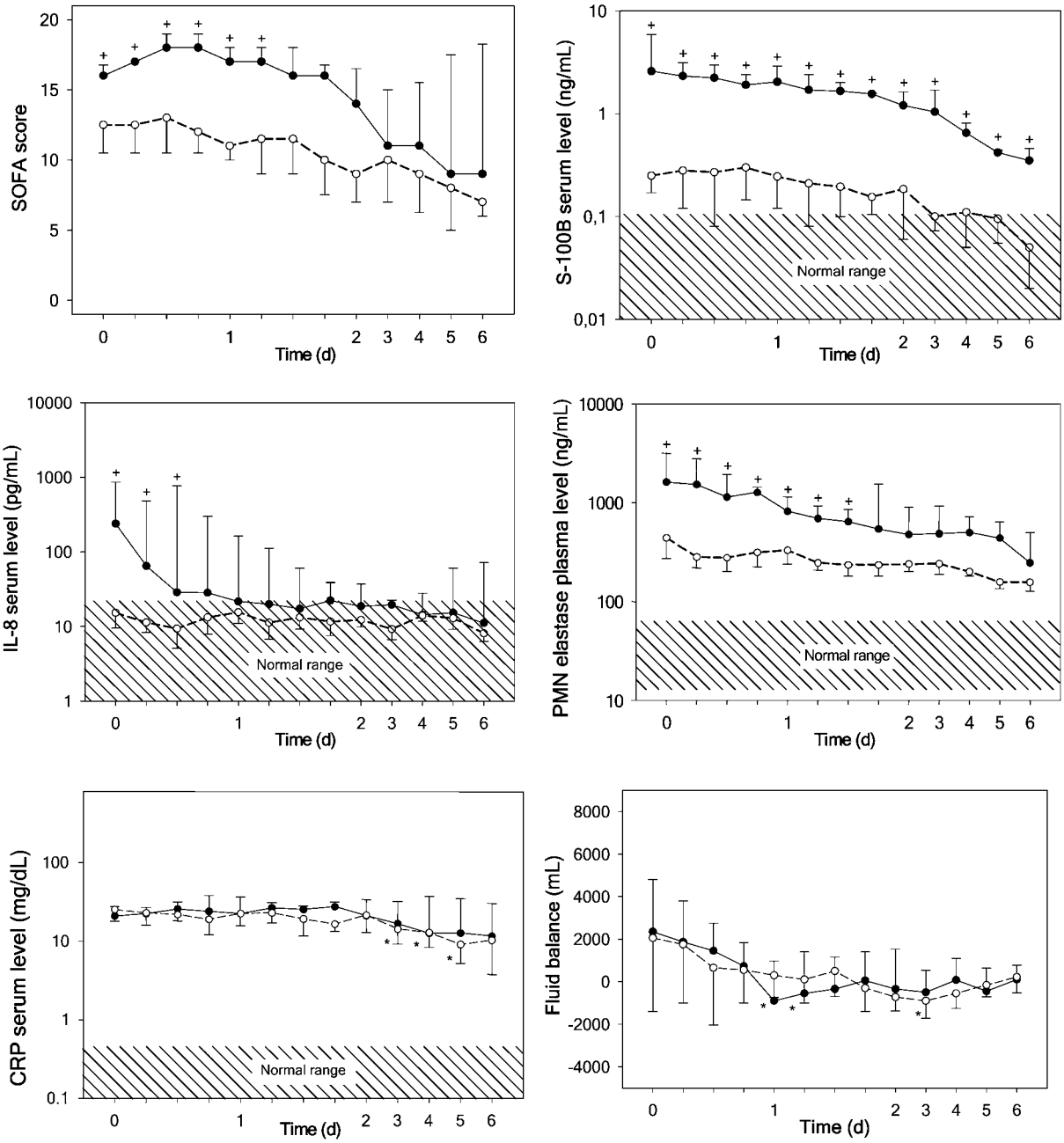

Figure 3 SOFA score, serum S-100B, IL-8, CRP, and plasma PMN elastase levels, as well as fluid balance within the first 6 days of septic shock. Patients were stratified in groups with an initial S-100B serum level >0.50 ng/mL ($n=8$; •; data are given as line and scatter plots presenting median and 75th percentile) or ≤ 0.50 ng/mL ($n=16$; ○; data are given as line and scatter plots presenting median and 25th percentile). $+p<0.05$ represents significant group differences between the two randomized groups.

of septic shock in the hydrocortisone group occurred more quickly than in the placebo group (2, 5, 6). However, during the observation period of 6 days, no significant difference concerning a decrease in the originally highly elevated S-100B serum levels were apparent when using hydrocortisone compared to placebo.

The exact mechanisms that lead to similarly high S-100B serum concentrations, particularly in the initial phase of septic shock, as in patients with severe head injury are still unclear. Neuronal cells, as well as damaged fat and muscle cells, must be considered as possible sources for the release of S-100B (41–43). Interestingly, patients with pathologically elevated initial S-100B serum levels of >0.50 ng/mL showed significantly higher median SOFA scores up to 30 h after study entry than those patients with initial levels ≤ 0.50 ng/mL. Moreover, individuals with clearly raised S-100B levels exhibited higher PMN elastase plasma levels until 36 h, whereas their IL-8 serum levels were elevated only up to 12 h after study entry. Although impairment of astroglial cells, possibly leading to prolonged neurological dysfunction, cannot be excluded as the primary origin of S-100B in the circulation, the systemic inflammatory process and peripheral tissue damage also have to be taken into

account as an additional cause for the different release pattern of S-100B protein (25, 41, 44).

In critically ill patients with septic syndrome, disturbance of the neurological functions can arise from a multitude of origins. Patients may have head injuries due to accidental trauma or can be intoxicated. Furthermore, they may suffer from prolonged shock in the case of severe systemic infection and may need to be resuscitated under sedation analgesia because of vasogenic reactions, myocardial dysfunction or coagulation disturbances (45). Particularly in the early phase of the disease, septic encephalopathy is quite difficult to diagnose in patients with concomitant disturbance of kidney or liver function, with metabolic collapse or with endocrine abnormalities due to the similarity to cerebral dysfunctions of other origins.

The early form of septic encephalopathy, which may not yet be accompanied by MOF, but probably only by the release of pro- and anti-inflammatory cytokines and their cytotoxic effects, is different from the late form, which is usually combined with MOF, hypotension, and other systemic symptoms. Septic encephalopathy is clinically characterized by disturbances of concentration and disorientation, as well as by delirium and coma in heavy cases. Encephalopathy may precede the leading symptoms of sepsis, and may thus be of special diagnostic value as a possible early marker of subsequent organ system failures (11, 12, 46). Radiological examinations, i.e., cerebral computed tomography (CCT), do not usually show any significant changes. Clinical evaluation can be achieved by means of electroencephalography (EEG) or the GCS score before sedation analgesia and intubation are applied.

The GCS score is frequently applied for the examination of cerebral dysfunctions. It correlates very well with the neurological long-term result in patients with severe head injuries, and can also be used for the evaluation of neurological dysfunctions in the long-term course of patients with MOF (15, 16). Eidelman et al. (14) reported increased mortality in 50 patients with septic encephalopathy in relation to the GCS score (16% at 15 points and 63% between 3 and 8 points). However, the clinical experience shows that the GCS score cannot always be estimated meaningfully in ICU patients with septic shock (30). Indeed, nearly all patients in our prospective randomized therapy study (5) were already sedated and ventilated for several days, and exhibited a continuous GCS score of 3 points when finally fulfilling the study entry criteria. Therefore, a valid neurological evaluation in the clinical process was practically impossible and the clinical diagnosis of septic encephalopathy would only have been possible by means of EEG. Yet, EEG was not typically applied due to the study design, for which measurements of S-100B serum levels were primarily not conceived (5).

In this situation, the introduction of a specific biochemical brain marker seemed to us to be of great interest for the retrospective diagnosis and prediction of septic encephalopathy in the long term. According to a recent study, the neuroprotein S-100B is expressed and released into the circulation not only in ischemic brain tissue damage after stroke or traumatic brain injury, but also during brain inflammation (47). Whether high local extracellular concentrations of S-100B have detrimental effects, such as the enhancement of apoptotic cell death, is still under debate (44). Therefore, we decided to evaluate S-100B serum levels in our patients with septic shock, whose serum samples were collected in the context of a prospective randomized study examining the effectiveness of hydrocortisone (1, 4, 5).

Although our data reveal for the first time the similar extent of systemic S-100B release after septic shock as after out-of-hospital cardiac arrest or traumatic brain injury, the main limitation of this randomized controlled study is the small number of patients. From this it follows that the study may be underpowered with respect to the ability to identify any significant differences concerning age, days of ventilation or mortality rate.

Conclusions

Hypercortisolemia induced by the infusion of stress doses of hydrocortisone differentially regulates the response of the neuroprotein S-100B and the inflammation markers IL-8 and PMN elastase in patients with hyperdynamic septic shock. In a randomized double-blind trial, we observed a significant reduction in IL-8 serum, but not in S-100B serum and PMN elastase plasma concentrations with time. For the first time, a similar extent of S-100B increase in serum of patients with septic shock at the time of primary diagnosis was shown as reported for out-of-hospital cardiac arrest or severe head injury. Although clinically relevant methods for judging brain damage in our septic shock patients are missing due to the study design, our data give clear hints for further prospective studies on S-100B serum levels in septic patients.

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