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HEMOFILTRATION DOES NOT INFLUENCE EARLY S-100B SERUM LEVELS IN SEPTIC SHOCK PATIENTS RECEIVING STRESS DOSES OF HYDROCORTISONE OR PLACEBO

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Abstract
Background: The prognosis in patients with hyperdynamic septic shock correlates with the presence and the severity of septic encephalopathy. However, the neurological evaluation is considerably influenced by the use of analgesia sedation during mechanical ventilation. An early concentration peak of the neuroprotein S-100B in serum reflects both cellular damage at an increased permeability of the blood-brain-barrier and a delayed renal elimination. Thus, the objective of this study was to analyze the effect of continuous veno-venous hemofiltration (CVVH) on early S-100B serum levels in septic shock patients, who were treated with either stress doses of hydrocortisone or placebo.
Methods: Twenty-four consecutive patients, who met the ACCP / SCCM criteria for septic shock, were enrolled in this prospective, randomised, double-blind, single-center trial. The severity of illness at recruitment was graded using the APACHE II and SAPS II scoring systems; the MODS was described by the SOFA score. All patients were prospectively randomised 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.
Results: Median S-100B serum levels of the hydrocortisone group decreased from 0.32 ng/ml (0.19–3.60) at study entry to 0.07 ng/ml (0.04–0.32) 6 days later without significant differences compared to the placebo group. Patients undergoing CVVH showed significantly higher S-100B serum values compared to patients without CVVH ($p<0.001$). However, initial median S-100B serum levels of the CVVH group even increased from 0.92 ng/ml (0.16 – 4.63) to 2.33 ng/ml (0.59 – 2.44) 30 hours after study entry, reaching data ranges already known in patients with out-of-hospital cardiac arrest or severe traumatic brain injury.
Conclusion: Early S-100B serum levels in septic shock patients receiving either stress doses of hydrocortisone or placebo were not influenced by CVVH. For the first time, we observed a similar extent of S-100B serum increase in CVVH patients, who had significantly higher S-100B serum values compared to those without CVVH, as reported for out-of-hospital cardiac arrest or severe traumatic brain injury. Hypercortisolemia induced by the infusion of stress doses of hydrocortisone did not significantly reduce early S-100B serum concentrations with time.

Key words: Septic shock; sepsis; hemofiltration; hydrocortisone; S-100B; brain damage

INTRODUCTION

Apart from multiorgan failure, critical illness myopathy or dysfunction of peripheral nerves, septic shock may cause serious brain damage and septic encephalopathy [11, 23, 24, 35]. Septic encephalopathy represents a cerebral malfunction, which may develop in the context of the systemic infection without a direct traumatic affection of the brain [12, 18, 26, 38]. Hereby, the prognosis of septic patients correlates with the presence and the severity 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 of the mortality rate was reported in relation to the Glasgow-Coma-Scale (GCS) score in patients with septic encephalopathy [18]. This score is still used for the evaluation of the neurological dysfunction and the prognosis throughout the course of multiorgan failure (MOF) [6, 27]. However, since the GCS score in septic shock is clearly influenced by the use of analgesia sedation during mechanical ventilation, an early biochemical marker should supply evidence for encephalopathy in the initial phase of sepsis, before clinical leading symptoms may occur.

The neuroprotein S-100B released into the circulation was considered as a reliable marker to detect brain damage due to isolated traumatic brain injury, stroke, hemorrhage or global ischemia [28-30, 36, 37]. Increased S-100B serum levels have been also observed to correlate with the duration of cardiopulmonary bypass surgery and the development of neurological complications [4, 9, 34]. Physiologically S-100B is localized in the cytosol or bound to the membranes of astroglial cells, mostly of the central nervous system [20]. If these cells are damaged, S-100B will be 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

minutes [25, 32]. An early concentration peak of S-100B in serum 20 minutes after brain damage seems to reflect both cellular damage at an increased permeability of the blood-brain-barrier [9] and a delayed renal elimination.

Thus, the objective of our study, which has been part of a single-center double-blind randomised controlled trial [13], was to analyze the effect of continuous veno-venous hemofiltration (CVVH) on early S-100B serum levels in septic shock patients, who were treated with either stress doses of hydrocortisone or placebo.

Materials and Methods

Study Design and Subjects

Patients 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 / Society of Critical Care Medicine Consensus Conference Committee: documented infection or positive blood culture; at least two symptoms of the systemic inflammatory response syndrome, i.e. 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/mm3 or < 4.000 cells/mm3 or immature neutrophils [bands > 10%]); evidence of organ dysfunction or hypoperfusion abnormalities; and the use of vasopressor support (norepinephrine or epinephrine at any dose, dopamine dose > 6 μg/kg/min) despite adequate fluid resuscitation. Only patients with high-output circulatory failure defined as cardiac index > 4.0 litres/min/m2 were studied. The hypercirculatory state had to be present without the use of positive inotropic agents such as dobutamine and dopexamine. The detailed study design and the patient routine treatment have been already described [13].

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 (SAPS) scoring 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. The Sepsis-related Organ Failure Assessment (SOFA) score, which was published in 1996 [33], was added to the study protocol by amendment and retrospectively calculated from the raw data.

The institutional review board of the Ludwig-Maximilians-University of Munich approved the study protocol. Relatives of the patients were informed regarding the medical problems, and the nature and purpose of the study as well and served as surrogates to determine the judgement 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 Anaesthesiology Munich-Grosshadern in the university hospital.

Intervention

Twenty-four patients were prospectively randomised 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 for 30 min, followed by continuous infusion of 0.18 mg/kg/h. After reversal of septic shock (defined as dopamine doses of < 6 mg/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 daily tapered off in 24 mg steps. Physiologic saline solution was used as placebo. To conduct the study in 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 [13].

For continuous veno-venous 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.

Treatment

Vasopressor therapy was titrated to achieve a mean arterial pressure (MAP) of > 70 mmHg. 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 randomisation, however, the attending physicians were free to use additional catecholamines such as epinephrine, dobutamine, or dopexamine. When septic shock reversed, norepinephrine or epinephrine were tapered off in steps of 0.02 to 0.03 μg/kg/min.

Infections were diagnosed according to clinical and microbiological criteria. Suspected infection at time of enrolment had to be 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.

During controlled ventilation and treatment with antibiotics, infusions, and systemic vasopressor support at the ICU, anaesthesia aiming to 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 examination of reflexes.

Blood Sampling and Biochemical Measurements

The first blood samples were taken at study entry at the ICU (point of measurement [PM] 1). Subsequently, blood samples were drawn every 6 hours (PM 2 – 9) during the next two days, and once a day throughout the following 4 days (PM 10 – 13). All specimens were converted to serum or citrated plasma, centrifuged with 3000 U/min for 10 minutes 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. To avoid interference with possible hemodilution, biochemical data were normalized to a total serum protein concentration of 70 mg/ml. For this reason, total serum protein of each sample was measured with a specific microprotein assay kit (BCA protein assay, code no. 23235; PIERCE, Illinois, USA).

Statistical analysis

All demographic and biochemical data are presented as median and interquartile range (25^{th} – 75^{th} percentiles). Group differences at each point of measurement were accomplished by means of Mann-Whitney-U test and Fisher´s exact test, respectively, due to missing 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 by means of generalized Wilcoxon (Breslow) test. Biochemical data of septic patients were compared to those reported of patients with patients suffering from out-of hospital cardiac arrest, patients with isolated severe traumatic brain injury (GCS score < 8 points), and healthy volunteers without history of brain or cardiac damage [21, 28, 29]. Blood sampling of the control groups was achieved after given informed consent. The statistical analysis was performed using SPSS version 12.0 (SPSS GmbH Software, München, Germany), a two-tailed p-value of < 0.05 was considered to indicate statistical significance.

Results

Characteristics of the Two Randomised Groups

Twelve patients each were assigned to the hydrocortisone-treated (H) and the placebo (P) group, respectively [13]. The characteristics of both patient groups did not differ according to the demographic data, the severity of the illness and the degree of the organ dysfunction (Table 1). In addition, no significant differences occurred concerning length of mechanical ventilation, administration of CVVH and survival rate after 28 days between the two subgroups. However, the median time of vasopressor support in the H group (2 days [IQR 1 – 6]) was significantly reduced compared to the P group (7 days [3 – 19]) in the ($p = 0.005$; Breslow test). Moreover, there was a trend to earlier resolution of the organ dysfunction syndrome in the H group [13]. The primary cause of septic shock was peritonitis in 9 patients (4 H / 5 P) and pneumonia in 13 patients (7 H / 6 P). One patient each suffered from meningitis and severe soft tissue infection, respectively.

S-100B Serum Levels of the Hydrocortisone-treated and the Placebo Group

Median S-100B, serum levels at study entry were considerably elevated for both groups, compared with values for healthy individuals (Fig. 1). After treatment with hydrocortisone, the S-100B serum levels of the H group were not significantly affected with time. Similarly, serum S-100B concentrations of the P group did not decrease significantly during the observation period.

Table 1. Characteristics of septic shock patients stratified into the hydrocortisone (n=12) and the placebo group (n=12). Age, scores and days of ventilation are presented as median and interquartile range (25% – 75% percentile).

Characteristics	**Hydrocortisone group (n=12)**	**Placebo group (n=12)**	**P-value**
Age (years)	41 (30 – 65)	54 (47 – 57)	0.410*
Gender (male : female)	7 : 5	6 : 6	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#
SOFA Score (points)	9 (7 – 12)	11 (9 – 14)	0.166#
Days of Ventilation	16 (12 – 24)	21 (8 – 38)	0.755#
CVVH (yes : no)	5 : 7	5 : 7	1.000
Mortality Rate (dead : alive)	3 : 9	5 : 7	0.514*

P-values describe statistical differences between both groups in the Mann-Whitney-U test;
* P-values for statistical differences in the Fisher´s exact test.

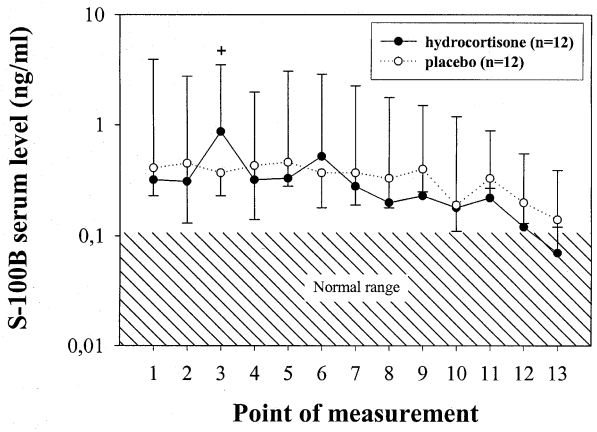

Fig. 1. Serum S-100B levels within the first 6 days of septic shock.
Patients are randomized in the hydrocortisone group (n=12; ●; data are given as line and scatter plots presenting median and 75th percentile) or the placebo group (n=12; ○; data are given as line and scatter plots presenting median and 25th percentile). The upper normal value of S-100B amounts to 0.12 ng/ml.
The first blood samples were taken at study entry at the ICU (point of measurement [PM] 1). Subsequent blood samples were drawn every 6 hours (PM2 – PM9) during the next two days, and once a day throughout the following 4 days (PM10 – PM13).
+ $p<0.05$ represents significant group differences between the two randomized groups. * $p<0.05$ shows significant differences compared to the baseline levels at study entry (PM1).

Median S-100B serum levels of the H group dropped from 0.32 ng/ml (0.19 – 3.60) at study entry to 0.07 ng/ml (0.04 – 0.32) 6 days later without significant differences compared to the P group. Only S-100B levels at PM3 (12 hours after study entry) with 0.87 ng/ml (0.14 – 2.63) were significantly higher for the H group than with 0.37 ng/ml (0.14 – 0.77) for the P group (Fig. 1).

Characteristics of the Study Subjects with or without CVVH

Septic patients undergoing CVVH (n=10) showed no statistical differences concerning age, gender, SAPS score, APACHE III score, hydrocortisone administration and days required for mechanical ventilation when compared to those patients without CVVH (n=14). However, the APACHE II score, the SOFA score and the mortality rate after 28 days were significantly higher in patients with hemofiltration, as expected (Table 2).

S-100B Serum Levels of the Study Subjects with or without CVVH

The CVVH patients exhibited clearly higher S-100B serum values up to PM11, and significant group differences to patients without CVVH became obvious with time except for PM 13 (Fig. 2). Median S-100B serum levels of the CVVH group even increased from 0.92 ng/ml (0.16 – 4.63) at study entry to 2.33 ng/ml (0.59 – 2.44) at PM6 (30 hours after study entry), but subsequently dropped to 0.02 ng/ml (0.01 – 0.27) 6 days after study entry.

Interestingly, the initial highly elevated S-100B values of CVVH group were within the data ranges recently demonstrated for patients with out-of-hospital cardiac arrest or severe traumatic brain injury [21,28]. Furthermore, median S-100B serum levels decreased to 0.02 ng/ml (0.01 – 0.27) in CVVH patients and to 0.10 ng/ml (0.05 – 0.30) in patients without CVVH at the end of the observation period, reaching data ranges of healthy controls with 0.04 ng/ml (0.01 – 0.08) [29].

Finally, median S-100B serum concentrations decreased significantly compared to the baseline levels after CVVH administration from PM12 onwards. And both groups reached the normal range at the end of the observation period (Fig. 2).

Table 2. Characteristics of the septic shock patients with (n=10) and without continuous veno-venous hemofiltration (n=14). Age, scores and days of ventilation are presented as median and interquartile range (25% – 75% percentile).

Characteristics	Hemofiltration (n=10)	No Hemofiltration (n=14)	P-value
Age (years)	45 (27 – 54)	54 (47 – 57)	0.096*
Gender (male : female)	7 : 3	6 : 8	0.285#
APACHE II Score (points)	29 (24 – 36)	22 (20 – 28)	0.031#
APACHE III Score (points)	111 (69 – 146)	79 (58 – 90)	0.074#
SAPS II Score (points)	66 (44 – 95)	50 (43 – 56)	0.138#
SOFA Score (points)	13 (12 – 16)	9 (6 – 10)	<0.001#
Hydrocortisone : Placebo	5 : 5	7 : 7	1.000#
Days of Ventilation	19 (5 – 30)	17 (12 – 28)	0.886#
Mortality Rate (dead : alive)	6 : 4	2 : 12	0.032*

P-values describes statistical differences between both groups in the Mann-Whitney-U test; * P-values for statistical differences in the Fisher´s exact test.

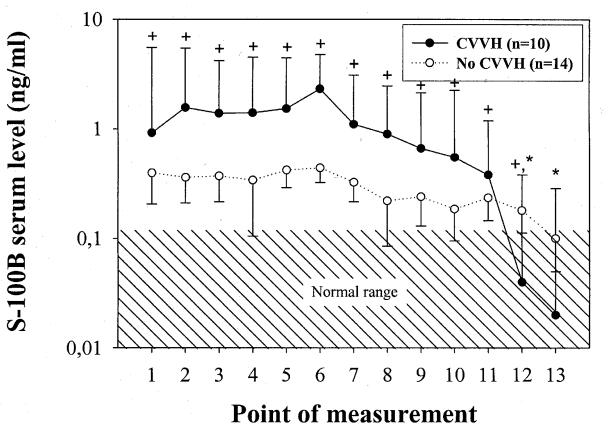

Fig. 2. Serum S-100B levels stratified in patient groups with (n=10; ●; data are given as line and scatter plots presenting median and 75th percentile) or without continuous veno-venous hemofiltration (CVVH; n=14; ❍; data are given as line and scatter plots presenting median and 25th percentile) during the first 6 days of septic shock.
Point of measurement see Fig. 1.
+ $p<0.05$ represents significant group differences between the two randomized groups. * $p<0.05$ shows significant differences compared to the baseline levels at study entry (PM1).

DICUSSION

The endogenous glucocorticoid hydrocortisone plays a pivotal role in the modulation of the immune response to sepsis [14]. Low--dose hydrocortisone infusions may attenuate the systemic inflam-matory response, as judged by clinical signs and inflammatory markers [3, 15]. Two double-blind, single-center trials demonstrated that stress doses of hydrocortisone reversed sep-tic 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 [10, 13]. Yet, during the observation period of 6 days no significant difference showed up concerning the decrease of the primarily highly elevated S-100B serum levels when using hydrocortisone compared to placebo.

The exact mechanisms, which 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 [2]. Although an impairment of astroglial cells possibly leading to prolonged neurological dysfunctions can not be excluded as primary origin for the S-100B in the circulation, the systemic inflammatory process and damage of peripheral tissue has also to be taken into account as an additional cause for the different release pattern of the S-100B protein [2, 17, 20].

Patients with septic encephalopathy frequently show increased serum urea and bilirubin levels, elevated APACHE II score values as well as a higher incidence of renal failure [18]. Prolonged kidney insufficiency means a retarded renal elimination of the neuroprotein S-100B, and as such persistently increased S-100B serum values. Continuous veno-venous hemofiltration (CVVH), which allows a better blood pressure control compared to other filtration techniques, has been reported to eliminate a variety of inflammatory mediators, which are excessively produced during sepsis, and which may ultimately lead to MOF [14, 19]. Therefore, the immediate CVVH after onset of septic shock should be also able to remove this protein (molecular weight of 21.000 Da) from the systemic circulation similar to creatinine and urea. Surprisingly, significantly higher S-100B serum levels were observed in patients with CVVH than in those without CVVH throughout the course of up to 6 days after onset of septic shock. Thus, despite of artificial kidney support the higher degree of septic syndrome in our patients needing CVVH, who revealed higher APACHE II and SOFA scores, seems to lead either to a longer lasting astroglial activation or to a more extended release from other extracerebral sources such as peripheral adipocytes, skeleton muscle cells or bone marrow [1, 2, 17, 20]. Nevertheless, these data are in line with a recently published, randomised controlled study revealing the effect of CVVH on the plasma concentrations of different humoral inflammatory mediators in septic patients [16]. In contrast to anaphylatoxins no substantial elimination of circulating cytokines could be achieved during septic MOF by zero-balanced hemofiltration [22]. Therefore, the CVVH in its present form can only be recommended as an additional therapy option in septic shock in case of simultaneous acute kidney failure to eliminate detrimental substances such as urea or bilirubin.

The early form of septic encephalopathy is quite difficult to be diagnosed in patients with concomitant disturbances of the kidney or liver function, with metabolic collapses or with endocrine abnormalities due to the similarity with cerebral dysfunctions of other genesis [5]. Septic encephalopathy may be 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 upcoming organ system failures [26, 31, 38]. Radiological examinations, i.e. cerebral computed tomography (CCT), usually do not show any significant changes. A clinical graduation can be achieved by means of electroencephalography (EEG) or the GCS score before sedation analgesia and intubation is applied.

The GCS score is frequently applied for the examination of cerebral dysfunctions. It correlates very well with the neurological long-term result and mortality in patients with severe head injuries, and can be also used for the evaluation of the neurological dysfunctions and in the long-term course of patients with MOF [6, 18, 27]. However, the clinical experience shows that the GCS score cannot always be estimated meaningfully in ICU patients with septic shock [7]. Indeed, nearly all patients of our prospective randomised therapy study [13] were already sedated and mechanically ventilated for several days and exhibited a continuous GCS score of 3 points at study entry. Thus, 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 usually not applied due to the study design, for which measurements of S-100B serum levels were primarily not conceived [13].

In this situation, the introduction of a specific biochemical brain marker seemed to us of high interest for the retrospective diagnosis as well as the prediction of septic encephalopathy in the long-term run. 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 [8]. 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 randomised study examining the effectiveness of hydrocortisone [3, 13, 14].

Conclusions

Although patients undergoing CVVH exhibited significantly higher S-100B serum values compared to those without CVVH, hemofiltration did not influence early S-100B serum release in septic shock patients receiving either stress doses of hydrocortisone or placebo. In this randomised, double-blind single-center trial, we observed a similar extent of S-100B serum increase in patients with septic shock at the time of primary diagnosis as reported for out-of-hospital cardiac arrest or severe traumatic brain injury. Hypercortisolemia induced by the infusion of stress doses of hydrocortisone did not significantly reduce early S-100B serum concentrations with time.

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